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Editorial

THE PROTOPLASMIC BASIS OF GLOMERULAR ULTRAFILTRATION

URINE formation begins with the passive process of ultrafiltration. Ludwig precociously suggested in 1844, that the glomerular capillaries function as mechanical filters. But, fully satisfying scientific proof of his theory was not forthcoming until, in our time, Wearn, Richards, and others after them adapted and used new quantitative physiologic and microchemical methods for the analysis of glomerular filtrates. The history of medical and biologic science makes it clear that major advances in basic problems of structure and function stem largely from use of appropriate new techniques and ideas. Even the brilliant Ludwig could not formulate his important theory until Bowman had made his amazingly detailed, accurate study of the Malpighian corpuscle. While Bowman, in turn, by the use of the greatly improved techniques and microscopes of the nineteenth century was enabled to see much more than the seventeenth century master, Malpighi.

Today's physical science and technology have produced an entirely new microscope, the electron microscope. Theoretically, this instrument is capable of resolving particles separated by only a few Ångström units. One Ångström unit is 0.0000001 mm., one ten millionth of a millimeter. Under especially favorable conditions, electron micrographs of useful magnifications of 1½ million diameters have been used to view structure at the molecular level in metallic crystals. Such extreme magnifications are not, at present, particularily informative or useful in the study of cellular structures, but magnifications of 100,000 diameters and more are usefully employed in biologic and medical research. The medical and biologic sciences have entered an era in which refined electronic instrumentation, and modern scientific techniques and ingenuity have made it possible to gain information about the ultrastructure and microbiochemistry of cells and their organized parts. As information of this type is obtained and effectively correlated, useful knowledge of vitally, and medically important cellular processes results. The new technique of electron microscopy of tissues has made notable advances in our knowledge of glomerular structure, which appear to have established a satisfactory basis for the understanding of the physical basis of glomerular ultrafiltration.

Electron microscopy has made it clear that the cells covering the glomerular capillaries, in all forms so far examined, from the marine dogfish to man, are not simple squamous, or cuboidal epithelial cells through which the glomerular filtrate must mysteriously ooze. Glomerular capillary walls of human, other

mammalian, avian, amphibian, and marine elasmobranch kidneys[1-9] are structurally specialized with channels and spaces, somewhat similar to those in a collodion membrane prepared for use as an ultrafilter. The relatively large spaces and channels appear to afford either immediate access or less direct, but free, access of the filtrate from the site of ultrafiltration to Bowman's capsular space. Since the energy for capillary filtration is supplied by cardiac action, the spaces and channels must serve merely as passive gutters to conduct the filtrate from it site of origin to capsular space.

The spaces and channels are formed by relatively large processes and folds, termed trabeculae, attached to the surface of the smooth, dense, homogeneous definitive glomerular capillary basement membrane, termed lamina densa. The processes and folds, or trabeculae, are formed by extensions of the protoplasm of the cells covering the glomerular capillaries. On the surface of the lamina densa, each trabecula gives rise bilaterally to a highly ordered series of remarkably uniform, minute protoplasmic processes, termed pedicels. Each pedicel is intermeshed between two neighboring pedicels, arising from the nearby proximate trabecula. The relationship is similar to that of the fingers, when one's hands are held in the same plane with the fingers extended and interdigitated. The intermeshed pedicels fill the entire area between the parallel, or nearly parallel, trabeculae, as the interdigitated fingers fill the space between the palms of the hands. Since the cells covering the glomerular capillaries appear to be structurally unique, they have been termed podocytes. The function of the podocytes appears to be as vitally important and physiologically precise as their structure is uniquely complex and highly ordered.

Except for the connection to its own trabecula of origin and its basal attachment to the lamina densa, the surface of a pedicel appears free. The entire surface, including the basal portion, of a pedicel possesses a well-defined, precisely limited, relatively impermeable cytoplasmic membrane. The limited capsular space which surrounds the free surface of a pedicel communicates freely, at times directly, in one direction with the main capsular space by means of the larger spaces and channels. In the other direction, it becomes extremely restricted to a uniform, continuous slit of molecular dimensions on the surface of the lamina densa. When the measurements are obtained from electron micrographs in which the shrinkage artifact has been minimized, the width of the slit and the fractional pore area that it forms on the surface of the lamina densa[4] appear to be significantly close to those required by filtration theory for a slit-pore capable of retaining the plasma proteins.[12,13] The evidence appears sufficient to support a working theory of ultrafiltration based on the ultrastructure and organization of the cells of the glomerular capillaries. In this theory of glomerular ultrafiltration, the mechanism chiefly responsible for the characteristics of the functionally determined limiting "pore" size is assumed to be the slit-pore formed by the close approximation of the surface cytoplasmic membranes of the podocytic processes on the definitive basement membrane of the glomerular capillary. It may be a surprise to some to think that living protoplasmic processes can form an efficient and precise ultrafilter capable, in health, of retaining plasma proteins. It will be less surprising to those acquainted with recent information afforded by the

electron microscope, which reveals that the surface membranes of many cells are orderly and frequently folded. This is especially true of glandular epithelial cells, such as the cells of the proximal tubule of the kidney.[10] Usually, the space between the folds of the surface membrane is extremely narrow and uniform. In the cells of the ciliary epithelium, the space between adjacent folds appears to be only 80 Å. wide,[11] and in electron micrographs of proximal tubule cells, showing little shrinkage, the space appears to be restricted nearly as much.[5] The uniform, narrow spaces formed by the opposed surface cytoplasmic membranes of the cells of the proximal tubule, in preparations showing little shrinkage, approximately meet the theoretical dimensions of a slit-pore capable of restricting the passage of plasma proteins by molecular sieving.[12,13]

The close embryologic relationship between the cells of the proximal tubule, and those of the visceral layer of Bowman's epithelium, which differentiate into podocytes, is well known.[14] In describing the cells of the proximal tubule and their prominent, so-called intracellular channels (better termed pseudo-intracellular), the writer observed that, "the interdigitation of the intricate cytoplasmic processes (forming the channels) is somewhat similar to the complex of processes and spaces formed by trabeculae and pedicels of the podocytes."[2] More recent studies[4] have extended the original observations, and fully support the suggestion that the processes of the proximal tubule cells which intermesh to form the relatively deep, but exceedingly restricted, spaces between the surface cytoplasmic membrane are homologous with the specialized trabeculae and pedicels of the podocytes. The unique morphologic adaptation of the podocyte is not so much the development of the folds and processes forming the trabeculae and pedicels, or their intricate complexity, as it is the specialization of the form of the folds and processes to make a precise molecular filter which at the same time has low resistance to flow and a high filtration rate. After years of fruitless searching for a restrictive mechanism responsible for glomerular ultrafiltration, and finally finding what appears to be a satisfactory mechanism, it was somewhat of a surprise, soon afterward, to recognize that the key to the secret of glomerular ultrafiltration was not only the long-looked-for restrictive mechanism itself. The great length of the slit-pore is a significant factor in the mechanism responsible for the high filtration rate of glomerular capillaries. Using Book's and Vimtrup's estimates of the total glomerular capillary surface area for two human kidneys, given by Smith,[19] and in the data on the slit-pore,[4] it is possible to calculate that the total length of the slit-pore may extend a distance of nearly 2,000, or even 4,000, miles. At magnifications of 150,000 used in electron micrographs of the slit-pore, these lengths approach the astronomical distance of the earth's orbit around the sun. The unique features of the glomerular ultrafilter include the great length of the ultrafiltration slit-pore (i.e., its area), and the obvious, even in the first electron micrographs, relatively large spaces and channels formed by the folds and processes of the podocytes. In mammalian glomerular capillaries, especially, it is the high filtration rate that is the unique functional characteristic, not the sieving of proteins. Similarly, the unique morphologic features of the glomerular capillary wall are twofold: first, the form of the podocyte and its processes, the trabeculae and pedicels, limiting the depth of

the slit-pore to only a few hundred Å. and rapidly expanding the space above the slit-pore to open grooves and free channels, leading directly to open capsular space, and second, the frequency and complexity of the folds forming the slit-pore, so that its total area is from 2 to 3 per cent of the glomerular capillary surface. The approximately 100 Å. width of the slit-pore is not unique. The glomerular ultrafiltration slit-pore appears to be merely a special case of the adaptation of a folded epithelial cell surface on the definitive basement membrane to form a molecular filter with a high filtration rate.

This high filtration rate is characteristic of mammalian glomerular capillaries, above all others. In the working theory for glomerular filtration, two cellular structural specializations, and a noncellular mechanism, appear to form the basis for ultrafiltration and the high filtration rates.[4] First, the podocytic ultrafiltration slit-pore, due to the uniform, somewhat triangular, cross-sectional profile of the pedicels, is restricted to molecular dimensions only near to the lamina densa. Second, the theory requires that the lamina densa be formed, wholly or in part, by a highly hydrated gel continuum, consisting of free and/or protein bound polysaccharides, which affords a pathway for relatively free diffusion and flow of water and solutes, without exercising a directional influence on the flow, or imposing a limitation of particle size in filtration as narrowly limited and well defined as that of the slit-pore. The more recent evidence from electron microscopy, even at the highest useful magnifications, fully confirm the common observation that the definitive basement membrane is homogeneous, without pores or fibrous structure capable of serving as an ultrafilter.[4] Previously described pores, spongy and fibrous structures[2,8,9] in this membrane are strongly suspect of being fixation and dehydration artifacts, similar to those which appear in a homogeneous, hydrated gelatin gel, when it is similarly treated.[15] Although there may be tenuous, fine proteinogenous filaments forming a framework in the membrane, with interstices too large to serve as the limiting pores, the evidence of modern histochemistry and electron microscopy are in full agreement in demonstrating the absence of typical collagen and reticular fibers in the definitive basement membrane, or lamina densa.

The third mechanism enabling the glomerular capillaries to filter at high rates is found in the attenuated endothelium lining the capillaries. Although fixation procedures and other technical factors may influence their apparent size, and even their apparent frequency,[16] electron micrographs usually reveal an astonishing number of relatively large holes, or fenestrations, in the attenuated lining endothelium, especially in mammalian glomeruli with high filtration rates.[3,4,7,8,9] If they exist in life and have diameters of dimensions approximately similar to those which appear in the electron micrographs, they would be several times too large to serve as endothelial ultrafiltration pores. In describing these apparent fenestrations of the attenuated lining endothelium, the writer suggested that if they exist in life they would serve to remove the barrier of the endothelial cytoplasmic membrane to the rapid flow of water and lipid insoluble materials through the glomerular capillary wall.[2]

The following evidence suggests that the endothelial fenestrations may be present and function in life. Using similar fixatives and technical procedures,

they are readily demonstrable in mammalian glomerular capillaries but not in muscles capillaries,[5 17] which have filtration rates estimated to be only 1/100 of the glomerular filtration rates.[13] The glomerular capillaries of the amphibia have relatively infrequent endothelial fenestrations when compared with those of mammals,[18] and their glomerular filtration rates are much less than those of mammals,[19] but higher than those of muscle capillaries. Finally, dogfish glomeruli with one of the lowest known glomerular filtration rates,[19] comparable in magnitude to that of muscle capillaries, appear to have no fenestrations.[5] Endothelial fenestrations, in perpendicular and tangential section, are bounded by cytoplasmic membranes, so that they do not appear to be mere fixation artifacts.[4,8,9]

Electron micrographs of well-fixed glomerular capillaries afford evidence of an additional mechanism for ultrafiltration, which is formed by the endothelial cells.[4] The more dense endothelial cell cytoplasm forms numerous folds and processes which appear to intermesh with each other, somewhat as the pedicels do, but with less frequency and complexity. There is a well-defined endothelial slit-pore, formed between the intermeshed endothelial cell processes, which has a sufficiently narrow width, in many sections, to restrict the passage of the plasma proteins. The endothelial ultrafiltration slit-pore may be confined to the folded borders of the endothelial cells, so that its total area is probably very much less than that of the podocytic slit-pore. Considering the limited area of the endothelial slit-pore, the net flow rate through it will be much less than that of the podocytic slit-pore. In tissue capillaries, or in glomerular capillaries with few or no endothelial fenestrations, the endothelial slit-pore probably functions as the chief flow route for water, electrolytes, and other lipid insoluble materials. In such capillaries the rate of flow may be expected to be much less than that of typical mammalian glomerular capillaries. Furthermore, since the plasma proteins would be retained by such capillaries, there is no necessity for an additional restrictive ultrafilter on the outside of the endothelial tube, such as occurs on the glomerular capillaries with endothelial fenestrations. The combined evidence from filtration data and electron micrographs of the glomerular capillaries, viewed in the light of modern filtration theory, as developed by Pappenheimer and associates[12,13] make possible the formulation of a working theory as to the mechanism of glomerular filtration.[4]

The maintenance of the precise width of a slit-pore, formed by many thousands of minute living protoplasmic processes, is likely to depend to a large extent upon the normal metabolism of the cells of which the processes are integral parts. It is known that ischemia is followed closely by proteinuria, and that the inability to retain proteins characterizes many diseases.[19] It is possible that some of the proteinuria may be related to impaired metabolism of the podocytic cells responsible for the maintenance of the ultrafiltration slit-pore. It is of suggestive significance that the proteinurias following ischemia and disease often reflect no permanent impairment of the filtration mechanism, and that plasma proteins are retained with normal efficiency, with recovery from the ischemia or the disease. It has been suggested[2] that disease or experimentally induced changes in the width of the pedicel may affect filtration rates. This suggestion has received support from electron micrographs of kidneys of nephrotic patients, in which

striking distortion and smudging of the podocytic processes was observed, even in those patients whose glomeruli showed no changes when examined with special techniques under the light microscope.[20] The pedicels of pathologic glomeruli of rats, in which Masugi nephritis had been induced, appear abnormal in electron micrographs.[21] Since the mitochondria of these pathologic podocytes also appear abnormal, it is possible that the toxic antikidney serum may damage the mitochondria sufficiently to impair the metabolic activities of the podocyte, which, it may be presumed, are required to maintain the normal, precise, and uniform shapes of the pedicels and trabeculae.

To complete this summary of the concepts of glomerular structure held by the author, a brief discussion of three additional aspects of the Malpighian corpuscle will be included.

Electron microscopy affords little support for the concept that there is a third cell type, the mesangial or interstitial cell in the normal glomerulus, or that there is a peculiarly limited space, which in a special sense may be considered to be an intercapillary space.[22] The evidence from the electron micrographs of thin serial sections supports the view that many, if not all, of the so-called mesangial cells are endothelial cells which have been sectioned obliquely, or tangentially, near the basement membrane.[2,3,4,14] All cells (except those belonging to the blood) within the boundaries of the capillary basement membrane in nondiseased glomeruli appear similar. Usually in thin serial sections, it may be demonstrated that they have a surface bordering the lumen. Exceptional cases in single electron micrographs may be seen, like that pictured by Yamada,[9] which fit the concept of a mesangium. However, the geometry of oblique sectioning is sufficient to afford an interpretation of an isolated section on the basis of the endothelial cells known to be present. The writer believes that an adequate series of sufficiently thin serial sections, which is not presently available, will supply the required evidence for, or against, the mesangial theory. It is to be hoped that this may be available in the near future. It is noteworthy that Zimmermann in developing the mesangial theory relied heavily on the embryologic concept that the Malpighian corpuscle is formed by the ingrowth of developing capillaries into the expanded end of the embryonic tubule.

Well over 100 years ago, Gerlach first suggested that the capillaries invaginated the tubule to form the two-layered Malpighian corpuscle. Gerlach stated that the capillaries were covered and supported as the mesentery covers and supports the intestinal loops. To the writer's knowledge, only three men have seriously questioned or denied the concept that invagination plays a dominant role in the development of the renal corpuscle: Herring (1900), Huber (1909), and Reinhoff (1922). Recent studies on the development of the rat glomerulus by the means of electron microscopy,[14] unequivocally support Herring's statement that, "the first appearance of the cavity of the capsule is a narrow slit and never a vesicle in the human kidney. Toldt's description of the driving in of one wall by the capillaries is not an accurate one. At this stage there are no capillaries in the glomerulus."[23] The weight of authority of a traditional concept which seems so obvious from inspection of the adult structure of the Malpighian body has prevented the recognition of the accuracy and signifi-

cance of Herring's studies. The evidence from the electron micrographs not only fully confirms Herring's studies, but also supplies important facts which Herring's excellent photographic and light microscopic techniques could not reveal. The electron micrographs establish that in the rat the glomerular capillaries differentiate in situ from an unorganized central mass of mesenchymal cells. Except for mitotic figures, all cells are similar in appearance. Differentiation of the capillaries seems to be dependent upon the influence of the maturing podocytes, which develop from Bowman's visceral epithelial layer. As the larger processes of the maturing podocytes elongate, they appear to separate the central mass of prospective endothelial cells into connecting groups, which appear in section to correspond to the basic patterns of the capillaries and lobules of adult glomeruli. The pedicels develop later on the definitive glomerular capillary basement membrane, or lamina densa. The lamina densa is not apparent in the earliest stages, but it forms later, as a relatively homogeneous structure between the cytoplasmic surface membranes of the podocytic processes and the endothelial cells. It closely follows the contours of the endothelial cell surface. The definitive basement membrane of the glomerular capillaries, once formed, changes little with normal aging. The basement membrane of Bowman's capsule first appears as a very thin structure in close relationship with the epithelial cells of the capsule, and increases in thickness as it ages, to become characteristically thick and fibrous in the mature renal corpuscle. There are, then, not only functional differences in the two basement membranes, but developmental and structural differences. Some fortunate sections of the junction of the arteriole with Bowman's capsule have been photographed under the electron microscope.[5] They show an apparent discontinuity of the capsular and capillary basement membranes, in some cases. In others the homogeneous component of the capillary and capsular basement membranes may be continuous, but the capsular basement membrane usually appears to separate into many, thin, spreading layers whose connections to the capillary basement membrane are difficult to determine. The direct continuation of the definitive glomerular capillary basement membrane with the "elastic" lamina of the arteriole has been clearly demonstrated in electron micrographs. The facts are in full agreement with the concept that the renal corpuscle is not formed by simple invagination of a blind, expanded end of an embryonic tubule.

Perhaps one of the most surprising results of recent research on the glomerulus has been the complete confirmation of the early studies of Bowman and Ludwig, and others, on the branching of glomerular capillaries and their organization into lobules. They pictured the lobule as the functional circulatory unit of the glomerulus and indicated that glomerular capillaries branch repeatedly. This is in contrast with the view widely held today that glomerular capillaries are organized as simple, nonbranching hairpin loops.[24] The capillary loop concept and the concept that the glomerulus develops by the invagination of the capillaries into the expanded renal tubule were used extensively by Zimmermann, and more recently by others, to provide a developmental and anatomic basis for the origin and function of the mesangium, and its modern derivative, "intercapillary space."

The evidence of many hundreds of electron micrographs led the author to suspect the simple, capillary loop concept, so that glomeruli were injected with latex, dissected with microneedles to expose the lobules and capillaries, and photographed.[3,4] These photographs established that the capillaries within the glomerular lobules, at least of man, the rat, and the dog, branch and anastomose freely. It is clear in the rat and dog that within each lobule the capillaries are organized into functional systems with large lateral vessels directly communicating with each other at either end of the lobule where they connect with the arterioles. From the medial borders of these larger vessels, smaller and shorter vessels branch at nearly 90 degree angles in the plane of the lobule. When unfolded and flattened, the lobule has somewhat the appearance of a tennis racket with a handle at both ends. The length and width of a lobule greatly exceed its third dimension. In the glomerulus, the lobule makes a pronounced fold at the antivascular pole. The small capillaries, branching medially from the direct communicating vessels, may anastomose with each other, or with another direct communicating vessel in the lobule. Pressure within these laterally branching small vessels will be maximal and the volume flow through them minimal, since they connect at each end to larger vessels which have a direct connection to the afferent arteriole. Since the ends of the small, anastomosing capillaries are attached to large vessels (as rungs of a ladder are attached to its sides), and since the large vessels connect directly with the arterioles, only the pressure differences in the large vessels will induce flow in the small vessels. If the rate of flow in the large vessels is sufficient to produce axial streaming, which seems probable, then only plasma free of cells is likely to enter the small vessels, especially since they branch nearly perpendicularily from the large vessels.[3,4] Thus, as Pappenheimer and Kinter[25] have suggested for the whole kidney, within the confines of the glomerulus, itself, there appears to be an anatomic mechanism for the separation of the red cells from plasma. The organization of the capillaries within the lobule supports the possibility that skimming of plasma is an automatic phenomenon, constantly occurring at normal blood flows.[3,4] The effect of skimming is to increase the plasma volume within the glomerulus. Since the ultrafiltrate that can be produced by a capillary system is a function not only of the difference between hydrostatic pressure and oncotic pressure, but also of the volume of plasma in the system, any increase in plasma volume will effect a corresponding increase in the ultrafiltrate. It appears, then, that the efficiency of the ultrafiltration process derives not only from ultramicroscopic specializations of the capillary walls of glomeruli, but also from the gross anatomic organization within the lobule of the capillaries, themselves.

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Original Communications

TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY WITH PULMONARY STENOSIS

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COMPLETE transposition of the pulmonary artery and aorta is one of the commonest congenital cardiac anomalies associated with cyanosis, but it is rarely compatible with life beyond early infancy, unless associated defects which permit crossing of the circulations are present. Patients survive longest who have auricular and ventricular septal defects. The usual salient features of the condition are intense cyanosis combined with pulmonary plethora, the result of blood being injected into the lungs under high pressure by the left ventricle, and of a right-to-left ventricular shunt (Wood,[12] Astley and Parsons[2]). However, when pulmonary stenosis is associated with complete transposition, pulmonary oligemia is the rule and the clinical picture is therefore radically altered.

The object of this paper is to report the clinical and pathologic features, and the surgical treatment of a group of cases having in common the transposition of the great vessels and pulmonary stenosis with deficient pulmonary circulation. The series consisted of 8 patients, 5 males and 3 females, whose ages were 11 months, and 1½, 3, 3, 4½, 6, 7, and 8 years, respectively.

CLINICAL FEATURES

Cyanosis had been noted at or soon after birth and physical activity was severely limited. The younger children had experienced feeding difficulties due to dyspnea and were unable to stand or walk at the expected age. The older patients could walk only from 50 to 200 yards on the level. All but one were well below the expected height and weight for their age. Squatting on effort was noted in 3 cases. One patient had suffered a left hemoplegia.

Physical examination revealed gross cyanosis with clubbing of the digits, to the same degree in both hands and feet. The venous pulse was normal in height and quality in 7 cases, but in several the peripheral arterial pulses were of remarkably full volume. In 1 case there was visible pulsation of the dorsalis pedis and posterior tibial vessels. The finding of vigorous pulsation of

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the peripheral vessels suggested at once that the diagnosis was not the tetralogy of Fallot. Right ventricular hypertrophy was present in all cases and the second heart sound was loud and single in 7 of them.

In 6 cases there was a loud systolic murmur and thrill in the parasternal region, but in 1 case no murmur was heard and in another the systolic murmur was soft. The maximum intensity of the murmur was either in the left parasternal region or was poorly localized.

With two exceptions there was considerable polycythemia (hemoglobin was 154-190 per cent) and arterial oxygen saturation estimated by oximetry ranged from 50 to 73 per cent saturation.

CARDIOGRAPHY

The cardiogram showed evidence of gross right ventricular hypertrophy in all cases and evidence of auricular enlargement in 4 cases. Limb leads showed left axis deviation in Case 2, in which there was a single ventricle, and marked right axis deviation in the remainder.

RADIOLOGY

In all cases the lung fields appeared to be oligemic or showed stippled hilar shadows suggestive of enlarged bronchial arteries. In 2 cases the left lung alone appeared to be oligemic. The superior mediastinal shadow was wide in 4 cases, normal in 3, and narrow in 1 other. Cardiac enlargement was usually slight to moderate in degree and involved the right auricle and ventricle. In none of the patients could the main pulmonary artery be identified with certainty, and in all but 2 it was difficult to be certain of the presence of the left pulmonary artery. The right pulmonary artery was usually well seen.

The left middle third of the cardiac contour was concave in 3 cases, straight in 1, and convex in the remaining 4 cases. It was thought that the convexity might be due to a grossly enlarged right auricular appendage, to a dilated outflow pathway of the right ventricle, or to an abnormally placed ascending aorta. In Case 3 it was thought that the first explanation was the correct one, since the shadow did not appear to be continuous with the path of the aorta, whereas the right auricle was seen to be considerably enlarged. It was known that the right auricular appendage could occupy such a position (Figs. 5 and 6). This explanation was verified at operation in Case 3 when the right auricular appendage was found to lie just above the left. In Case 2 (Fig. 7) angiocardiography suggested that the shadow was caused by an enlarged ventricular outflow pathway and the autopsy findings supported this suggestion. In Case 1 (Fig. 1) it was not possible to decide which structure formed the contour of the middle third of the left cardiac border. The conventional radiological findings are illustrated in Figs. 1, 2, 3, and 4, and summarized in Table I.

Angiocardiography was performed in 5 patients and was valuable in demonstrating the abnormal position of the aorta. In the lateral projection it lay anteriorly in front of the pulmonary artery (Figs. 5 and 6), and in the anteroposterior projection it could be seen arising from the

TABLE I. RADIOLOGY

CASE	PULMONARY OLIGEMIA	SUPERIOR MEDIASTINUM	HEART SIZE	M.P.A.	L.P.A.	R.P.A.	LEFT MID THIRD
1	L	Narrow	+	O	Small	Small	Convex
2	L	Normal	++	O	Small	Small	Convex
3	R & L	Wide	N	O	O	Small	Convex
4	R & L	Normal	++	O	O	Small	Concave
5	R & L (Bronchial supply)	Wide	+	O	O	N	Concave
6	R & L	Wide	+	O	O	O	Concave
7	R & L	Wide	++	O	O	O	Straight
8	R & L	Normal	+	O	O	Small	Convex

outflow pathway of the right ventricle (Figs. 7 and 8). The main pulmonary artery could not be seen in 4 of the 5 cases, and in 2 of these the left branch also was not seen, although at operation the vessels were found to be present in all cases. It follows that failure to opacify the main pulmonary artery or its left branch cannot be used as evidence of atresia.

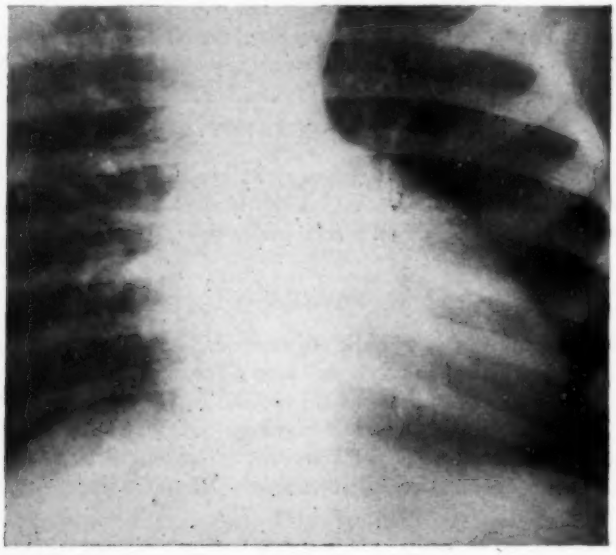

Fig. 1.—Case 1. A 6-foot posteroanterior chest radiograph. The shadow of the great vessels is narrow, and there is moderate cardiac enlargement. The left middle third of the cardiac contour is convex and the left lung appears to be oligemic. The main pulmonary artery cannot be defined with certainty.

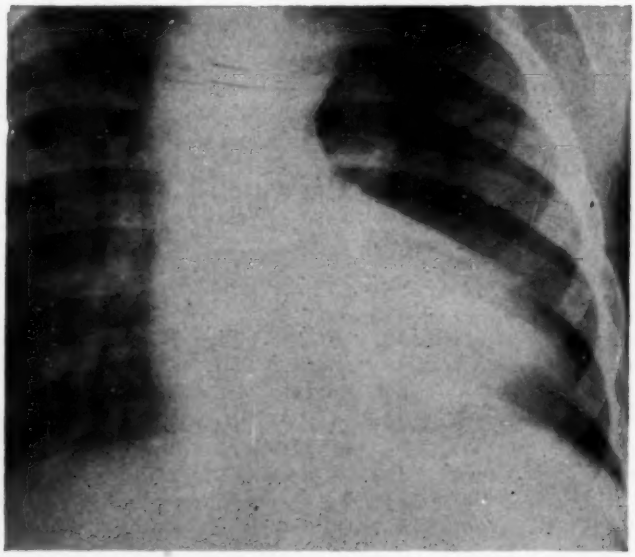

Fig. 2.—Case 4. A 6-foot posteroanterior chest radiograph. There is considerable cardiac enlargement and a prominent aorta. The left middle third of the heart shadow is concave and the main pulmonary artery cannot be distinguished. The left main branch cannot be identified with certainty but there is a vascular shadow at the left hilum. The lungs are oligemic.

CARDIAC CATHETERIZATION

Cardiac catheterization was performed only in Case 7, because the pulmonary arteries could not be identified with certainty radiologically. Neither the aorta nor pulmonary artery was entered, and the investigation contributed nothing except confirmation of right ventricular hypertension.

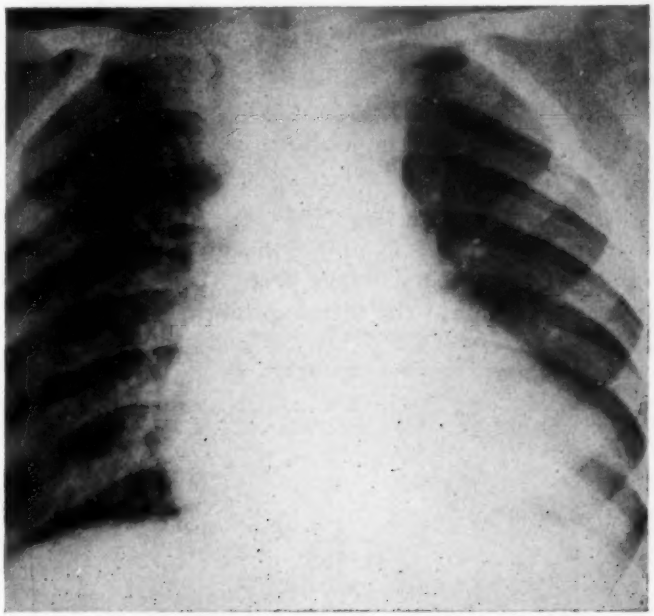

Fig. 3.—Case 7. A 6-foot posteroanterior chest radiograph. There is considerable cardiac enlargement and a wide superior mediastinal shadow. The left middle third of the cardiac contour is straight but neither the main pulmonary artery nor its right and left branches can be seen. Pulmonary vascular markings are more conspicuous on the right than on the left.

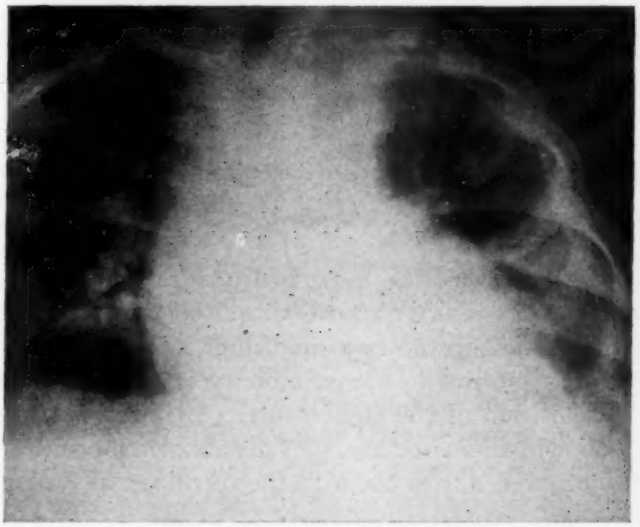

Fig. 4.—Case 5. A 6-foot posteroanterior chest radiograph. There is a wide mediastinal shadow. The stippled lung markings are suggestive of enlarged bronchial arteries.

DIFFERENTIAL DIAGNOSIS

Differentiation from the tetralogy of Fallot is difficult. In both conditions cyanosis appears early and capacity for effort is greatly reduced; in both there is right ventricular hypertrophy, a basal systolic murmur, and diminished pulmonary blood flow. However, suspicion that the condition was not Fallot's tetralogy will be aroused by the finding of a loud single second sound at the "pulmonary area." This is unusual in Fallot's tetralogy in which the aortic component of the second sound is not particularly loud and the pulmonary component, though it may be quiet and delayed, can often be heard. In transposition with pulmonary stenosis, the loud single sound is probably produced by aortic valve closure, which is well heard at the second left intercostal space owing to the anterior position of the transposed aorta. Pulmonary valve closure is inaudible, presumably owing to the posterior position of the pulmonary artery as well as to the very low pulmonary artery pressure. The presence of exuberant arterial pulses is most unusual in the tetralogy and should suggest transposition.

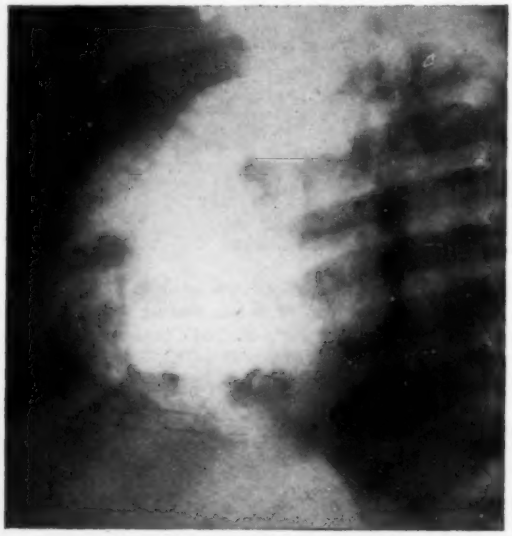

Fig. 5.—Case 6. Lateral angiocardiogram at 3 seconds showing the aorta arising anteriorly from the right ventricle. The right auricular appendage is enormously enlarged and is in the position normally filled by the right ventricular outflow tract and pulmonary artery. The pulmonary artery is not opacified. There is a large right-to-left shunt at ventricular level.

On conventional radiology the heart in transposition may be larger than is the rule in Fallot's tetralogy. Angiocardiography, however, is the most dependable method of differentiating the two conditions. It shows the abnormal position of the aorta lying anterior to the pulmonary artery in the lateral projection and occupying the position of the right ventricular outflow tract in the anteroposterior view (Goodwin and associates[8]). This abnormal position of the systemic outflow tract is considered not to occur in the tetralogy of Fallot (Goodwin and associates[9]).

Differentiation from pulmonary atresia may be difficult when there is no systolic murmur, and when the pulmonary arteries cannot be seen with certainty

either in the skiagram or by angiocardiography. In such cases if the diagnosis is seriously in doubt, cardiac catheterization may be indicated. It may, however, be impossible to pass the catheter through both a ventricular septal defect and a stenotic pulmonary valve. Uncertainty would then remain and a definite diagnosis would depend on exploratory thoracotomy.

The condition may require differentiation from certain types of persistent truncus arteriosus in which there is diminished pulmonary blood flow. Such cases may have a loud single second sound at the second left intercostal space, but the murmur of pulmonary stenosis is not present. On angiocardiography the appearance of a transposed aorta may be simulated by a truncus, but if the pulmonary artery can be seen to arise from the left ventricle, the diagnosis becomes clear. The demonstration of a definite right branch of the pulmonary artery on straight radiography or angiocardiography is a point against the diagnosis of pulmonary atresia or persistent truncus arteriosus.

Fig. 6.—Case 7. Lateral angiocardiogram at 5 seconds showing the aorta arising anteriorly from the right ventricle and an enlarged right auricular appendage lying in front of the aortic root. The left ventricle and interventricular septum can also be seen. There is a large shunt at ventricular level. The pulmonary artery is not opacified.

Examples have been reported of transposition of the great vessels in association with normal or underfilled lungs, but without pulmonary stenosis or atresia. In such cases the two circulations cross by way of a patent foramen ovale and ductus arteriosus; the flow through the latter is from pulmonary artery to aorta, and this prevents overfilling of the lungs (Astley and Parsons[2]). One of us (J.F.G.) has seen 2 infants with a syndrome differing from that described

by Astley and Parsons only in that there was present a ventricular septal defect instead of a patent foramen ovale. In both of these cases there was greater cyanosis of the hands than of the feet and this enabled the correct diagnosis to be made, although no continuous murmur was heard. Both subjects died in infancy, and autopsy confirmation of the diagnosis was obtained. If, however, such differential cyanosis is absent, this syndrome may be indistinguishable from transposition with pulmonary stenosis.

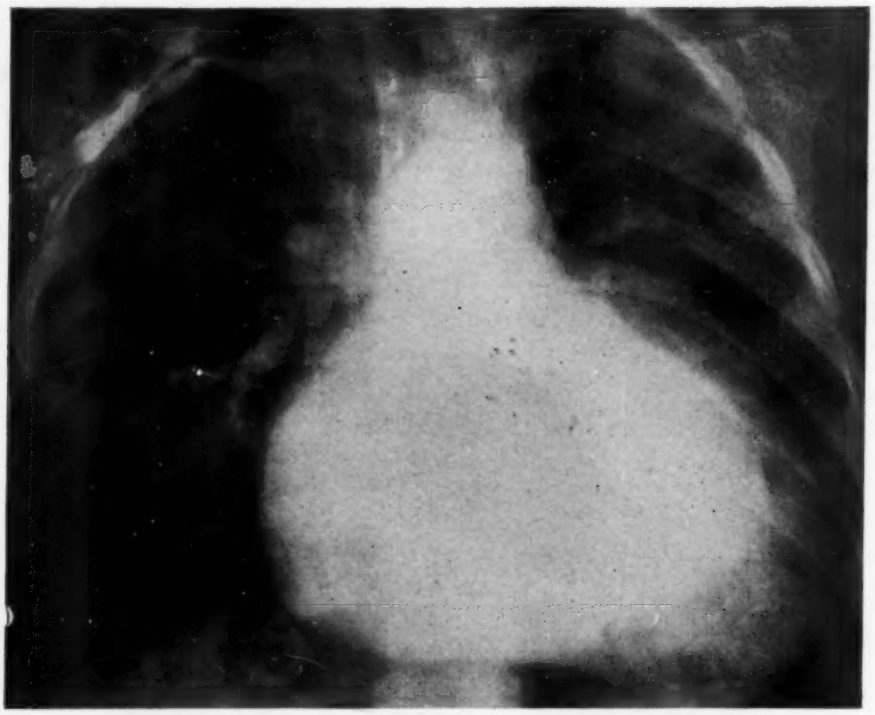

Fig. 7.—Case 2. Anteroposterior angiocardiogram at 4 seconds showing a large single auricle and the abnormal position of the systemic outflow tract, which arises from the "right" ventricle. The convexity of the left middle third appears to be due to a hypertrophied "right" ventricular outflow tract. The right pulmonary artery is opacified but the main trunk and its left branch are not seen. There is a large shunt at ventricular level.

SURGICAL TREATMENT

In the early cases of this series the decision to perform a thoracotomy was taken on empirical grounds. The patients were severely handicapped and were beginning to deteriorate. Their skiagrams showed oligemic lungs, and, although complicated malformations were suspected and the presence of a patent pulmonary artery was uncertain, it was nevertheless felt justifiable to perform a thoracotomy in the hope of finding vessels suitable for systemic-pulmonary artery anastomosis. After Blalock's operation had been seen to produce conspicuous benefit in Case 3, confidence in the recognition of the syndrome and the desirability of surgical treatment was greatly increased and thoracotomy was ultimately performed in all 8 patients. In 7 of the patients a subclavian-pulmonary

artery anastomosis was performed, and in 1 of them an aorto-pulmonary artery anastomosis. Five patients survived operation; in these a thrill was palpable over the anastomosis, and a continuous murmur became audible over the chest. The period of follow-up in these cases has been 1 month, 1 year, 18 months, 2 years, and 2½ years, respectively. Four patients have a considerably increased capacity for effort since the operation. One child (Case 3), previously unable to walk, is able to run short distances and walks indefinitely on the level; another (Case 7), who previously squatted frequently while walking, can now run 100 yards and can carry on a conversation immediately afterwards. Case 4, previously able to walk only 20 yards, can now walk a half mile and can run short distances. Case 6 was 3 years old at the time of operation and was then able to walk only a few steps. One year later he was walking without difficulty. The remaining patient (Case 8) is markedly improved, 1 month after operation.

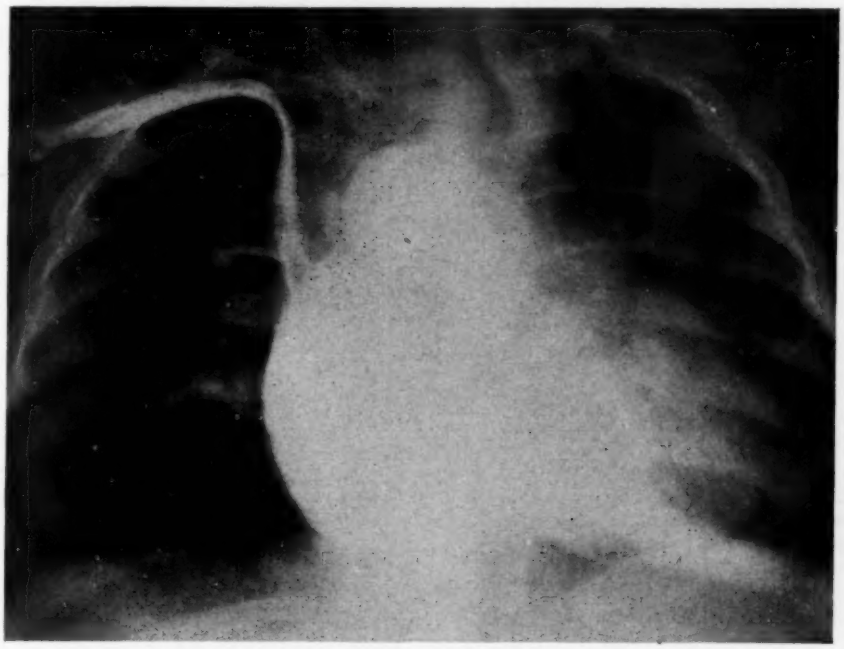

Fig. 8.—Case 5. Anteroposterior angiocardiogram at 2 seconds showing the abnormal origin of the aorta from the right ventricle. The pulmonary arteries are not opacified. The arteries arising from the aorta are large and tortuous.

In contrast to these striking changes in physical capacity there has been little change in hemoglobin level and only slight diminution in cyanosis. This, however, is not surprising since the aorta arising from the right ventricle continues to receive a large proportion of venous blood.

Three patients died following thoracotomy. In Case 2 the subclavian artery was unsuitable for a Blalock anastomosis, and, therefore, an aorto-pulmonary artery anastomosis was attempted. Cardiac arrest occurred before the anastomosis could be completed. In Case 5 the anastomosis was probably inadequate owing to the small size of the subclavian artery. The child's general condition had been extremely poor prior to operation, and she died a few hours after its

completion. The third fatality (Case 1) occurred quite unexpectedly on the second day following an apparently successful subclavian-pulmonary anastomosis. No explanation for this was found at autopsy.

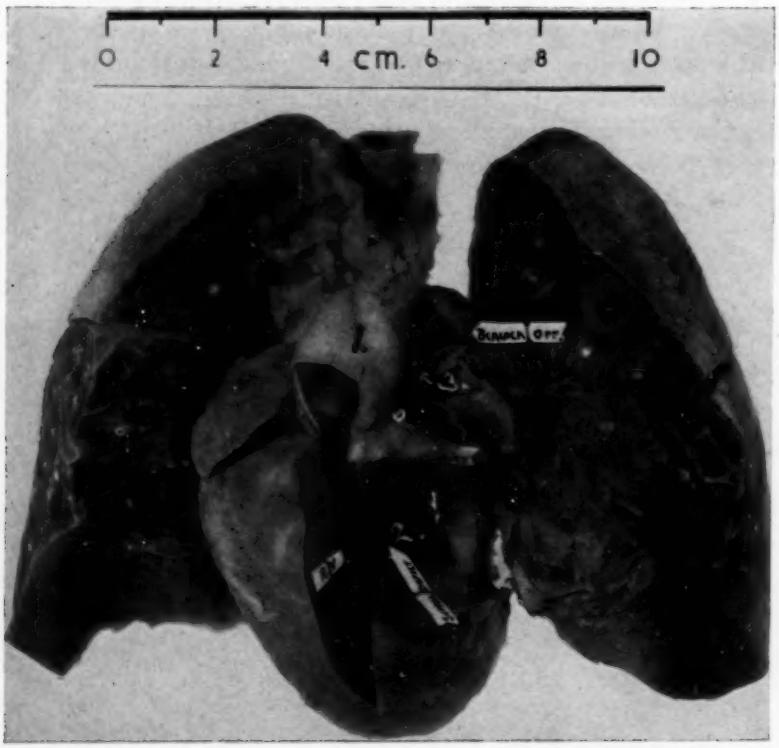

Fig. 9.—Case 1. Autopsy specimen. A greatly hypertrophied right ventricle (*RV*) gives rise to the aorta (*1*). There is a ventricular septal defect (*2*) measuring about 1 cm. in diameter. Behind and to the left of the aorta, the pulmonary artery (*3*) arises from the left ventricle. A subclavian-pulmonary artery anastomosis has been performed.

MORBID ANATOMY

In all 3 patients studied at autopsy, the diagnosis of transposition with pulmonary stenosis was confirmed. The aorta arose entirely from the right ventricle, the pulmonary artery entirely from the left, and the pulmonary valve stenosis was present in each instance. Associated defects, however, differed from case to case.

In Case 5, the auricular septum was almost entirely absent but the ventricular septum was normal. There was considerable right ventricular hypertrophy, the conus region being 11 mm. thick. The pulmonary "valve" consisted of a diaphragm with a slightly irregular perforation of about 15 mm. circumference, just proximal to a small, blind saccule.

In Case 1 there was merely a slit patency of the foramen ovale, but a rounded defect 1 cm. in diameter was present in the upper part of the interventricular septum (Fig. 9). The right ventricle was considerably hypertrophied and gave rise to the aorta which was about twice the diameter of the pulmonary artery which arose from the left ventricle. The pulmonary valve had 3 cusps, 1 of which was malformed and consisted of a thick fibrous nodule about $5 \times 3 \times 3$ mm., which partially obstructed the first part of the pulmonary artery. The bronchial arteries were greatly enlarged, the supply to the left lung being more profuse than that to the right side (Cudcowicz and Armstrong[7]).

In Case 2 the heart was biloculate (Fig. 10). The common auricle appeared to consist mainly of a right auricle with a left auricular appendage attached. The systemic and pulmonary veins were normal. The common auricle opened through a 3-cusped valve into a single ventricle 8 to 10 mm. thick. The great vessels arose in transposed positions, the aorta arising above and to the right of the pulmonary artery. The pulmonary "valve" was a conical structure measuring 8 mm. at its base and 2.5 mm. at the apex. The bronchial arteries were greatly enlarged.

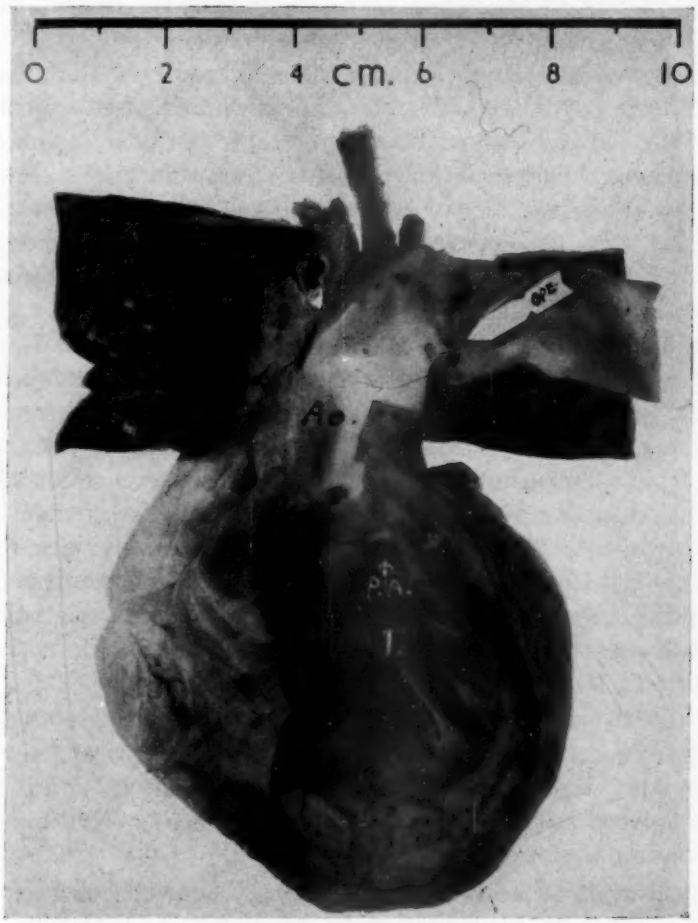

Fig. 10.—Case 2. Autopsy specimen. The heart is biloculate and a 3-cusped valve (*1*) can be seen opening into the single ventricle. The aorta (*AO*) and pulmonary artery (*PA*) arise in transposed positions; the pulmonary valve, through which a rod has been passed, is stenotic and lies below and to the left of the aorta. A white marker shows the site of the aorto-pulmonary anastomosis (Potts operation).

DISCUSSION

The association of pulmonary stenosis or atresia with transposition is rare. Abbott[1] described 1 case in which there was stenosis of the conus of the right ventricle and multiple associated anomalies. Taussig[11] in discussing extreme pulmonary stenosis or atresia associated with extreme dextroposition of the aorta mentioned 4 cases, 2 with pulmonary atresia, and 2 with pulmonary stenosis. In only 2 cases, however, was there complete transposition of the great vessels;

the pulmonary artery arose from the right ventricle, and the aorta was extremely dextroposed in the other 2. All cases were associated with a ventricular septal defect and 1 with a patent ductus arteriosus. Campbell and Suzman[5] described 2 cases of transposition with pulmonary stenosis, 1 with associated auricular and ventricular septal defects, and the other with a single ventricle (Campbell and associates[6]). Astley and Parsons[2] mentioned 2 cases in a series of 16 patients with complete transposition, and Keith and associates[10] listed 2 in a series of 62 cases of partial or complete transposition.

Taussig[11] as well as Campbell and Suzman[5] considered that the presence of pulmonary stenosis greatly modifies the clinical picture of transposition, and we would agree with Taussig that such cases resemble the tetralogy of Fallot rather than transposition. Differentiation depends chiefly on the presence of a loud single second sound in the second left intercostal space, exuberant arterial pulsation, and the angiocardiographic demonstration of an abnormally placed systemic outflow tract in the posteroanterior view, with an anterior position of the aortic root in the lateral view.

The cardiogram is of no help in differential diagnosis. In 7 of our cases it showed right ventricular hypertrophy with right axis deviation, while in the remaining case there was right ventricular hypertrophy with left axis deviation. The association of central cyanosis with left axis deviation is virtually pathognomonic of tricuspid atresia, but the combination of right ventricular hypertrophy, left axis deviation, and central cyanosis may occur in Eisenmenger's disease and truncus arteriosus, as well as in single ventricle. Left axis deviation and cyanosis, with incomplete right bundle branch block, or "balanced" ventricular complexes over right and left ventricles may occur in atrioventricularis communis, situs inversus with levocardia, or hypoplasia of the right ventricle without tricuspid atresia (Brink and Neill[4]).

In our case, left axis deviation was associated with a single ventricle. This association, however, is inconstant; Campbell and associates[6] found it in only 1 out of 6 cases with single ventricle and pulmonary stenosis, and it was absent in 1 case with single ventricle, transposition, and pulmonary stenosis (a case otherwise closely resembling ours).

The appearances on conventional radiology showed considerable variation (Table I). Taussig[11] has suggested that narrowness of the shadow cast by the great vessels in the posteroanterior view is a valuable sign of transposition. Astley and Parsons,[2] however, found it in only 4 out of 14 cases. It was present in only 1 of our 7 cases (Fig. 1), and in 4 cases the superior mediastinal shadow was actually wider than normal (Figs. 3 and 4).

Convexity of the left middle third of the cardiac contour has been thought to be due to the abnormal position of the ascending aorta (Astley and Parsons[2]), and this explanation appeared to hold good for one of our patients (Case 6). It has also been suggested that the left ventricle may cause the convexity (Keith and associates[10]). We have not seen this, but in one case angiocardiography and autopsy showed that the right ventricle was responsible for the shadow (Case 2, Figs. 7 and 10). In a third patient who showed the convexity, neither of these explanations seemed applicable and it was suggested that a greatly enlarged

right auricular appendage was responsible for the shadow. Operative findings supported this opinion (Case 3).

In none of our cases could the main pulmonary artery be seen in the skiagram, and in 2 cases neither of its main branches could be detected. This was of considerable importance in diagnosis and in the planning of surgical treatment. It was not always clarified by angiocardiography, for in 2 of our cases neither the main pulmonary artery nor its left branch were visualized, although they were subsequently found to be present at thoracotomy. Failure of opacification of these vessels may have been due partly to the posterior position of the main pulmonary artery and to the small size of its branches; but probably it was due mainly to the passage of the bulk of the contrast medium directly from the right ventricle to the aorta. It must, therefore, be emphasized that failure to demonstrate the pulmonary arteries cannot be used as evidence of their absence.

It seems unlikely that cardiac catheterization would be of much help in this problem, since passage of the catheter through the ventricular septal defect and then through a pulmonary stenosis would presumably be a very difficult matter, and inability to do so could not be used as evidence of absence of the pulmonary artery. It is possible that cineangiography might be helpful, but we have not yet had an opportunity to apply this technique in such cases. Meanwhile, it would seem that if the patient is severely handicapped and the diagnosis otherwise seems probable, an exploratory thoracotomy is justified despite the fact that the pulmonary arteries have not been demonstrated with certainty.

It is probable that the success of the operation depends partly upon the presence of sufficiently large septal defects to permit the increased flow of oxygenated blood entering the left heart to pass to the right ventricle and thence to the aorta. If such defects are inadequate, the operation may prove of little benefit, or even be harmful, as the left ventricle may prove unequal to the demands presented by an increased output in the face of pulmonary stenosis. However, this does not seem to have occurred in our unsuccessful cases, in none of whom was there clinical or autopsy evidence of left ventricular failure. It is probable that if the septal defects are sufficiently large to allow the child to reach the age of 1 or 2 years, they will be found to be adequate to meet the demands created by a systemic pulmonary anastomosis for at least 1 year (the shortest follow-up period in our series) and possibly for much longer.

The benefit produced by anastomonic operations in our series has been considerable. There is little mention of similar experience in the literature. Campbell and Suzman[5] mentioned 2 cases in which thoracotomy was performed, but apparently no operative correction was attempted. Astley and Parsons[2] briefly quoted a case in which a subclavian-pulmonary artery anastomosis was performed by Mr. d'Abreu, with an excellent result, but they gave no details. In our 5 patients who survived operation there has been a striking increase in capacity for effort—children who previously squatted frequently and walked with difficulty have become able to run short distances and to walk on the level without difficulty. The operation, however, may carry a higher mortality perhaps than in the tetralogy of Fallot, although our series is too small to be sure of this. But the great benefit which can be produced in the face of an otherwise very poor prognosis certainly makes the risks worth while.

SUMMARY

Eight cases of transposition of the great vessels with pulmonary stenosis are reported. The clinical features, radiologic findings, and cardiographic changes are described and the differential diagnosis is discussed with special reference to the clinical features and to angiocardiography.

All patients were undersized, severely handicapped by dyspnea, and intensely cyanosed. A subclavian-pulmonary artery anastomosis was performed in 7 cases and an aorto-pulmonary anastomosis in 1 case. There was striking improvement in the physical capacity of 4 patients, who were followed up for periods ranging from 1 to 2½ years; 3 patients died at, or soon after, operation; only 1 month has elapsed since operation in the remaining patient, but she has improved.

It is concluded that the malformation produces a syndrome which can be diagnosed with reasonable accuracy on clinical and angiocardiographic grounds. Treatment by systemic-pulmonary artery anastomosis carries a considerable risk, but it offers a chance of great improvement in severely handicapped patients whose prognosis is otherwise very poor.

We wish to thank Dr. R. E. Bonham Carter, Dr. Trevor Mann, Dr. Mary Wilmers, and other physicians who very kindly referred patients to us.

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CARDIAC DILATATION AND HYPERTROPHY

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BASIC information about the nature and origin of cardiac hypertrophy is lacking.[1] One theory of the origin of cardiac hypertrophy was proposed by Eyster in 1927.[2] Poorly documented, not confirmed in certain aspects by experiment, and contrary to clinical experience, the theory has, however, persisted in widely used textbooks.[3-7] The purpose of this communication is to review evidence about this theory and to report the inability to confirm results indicated by Eyster when the crucial experiment supporting the theory was repeated.

In contrast to the work-hypertrophy theory, Eyster proposed that injury to the heart's fibers initiated a process leading to hypertrophy. The injury, he stated, was consequent to cardiac dilatation. After dilatation, hypertrophy followed in a perpetuating fashion, even though the cardiac work load causing the dilatation was removed.

Eyster based his theory on canine experiments.[2,8,9] In these, a rubber tie was placed about the dog's ascending aorta and constriction produced. When the tie was left in place for a month or more, it was reported that cardiac hypertrophy developed. When the tie was removed after 3 to 6 days, at the height of dilatation, it was believed that hypertrophy developed at the same rate as if the tie were still in place. It is this experiment which has been repeated with the results to be presented below. Ancillary experiments were performed by Eyster, indicating that cardiac hypertrophy followed cardiac dilatation produced by massive blood transfusions. Necessary data to support the theory were not published.

EYSTER'S EXPERIMENTS

In 1927,[8] results were reported from placing a constricting tie about the aorta in 28 dogs. Seven died from too great constriction, and 3 from other operative causes, leaving 18 animals for observation with the tie left in place. X-rays to determine the area of the frontal cardiac silhouette were made at various intervals following operation. Unfortunately, few films were taken soon after operation to study cardiac dilatation. Twelve animals had no x-rays until 14 days after operation. Only 3 animals were x-rayed more than 5 times during the period of the experiment. Two of these showed no evidence of a phase of dilatation, in

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spite of final increases in the areas of the frontal cardiac shadows. There is but one dog (No. 2) whose x-ray areas indicated dilatation and recovery from dilatation followed by hypertrophy, stated to be characteristic of this group. The average increase in size of the cardiac silhouette for 18 dogs was 10.5 per cent. The accuracy of the method was indicated to be 5 per cent.[10] Autopsies were performed on 10 dogs. In general, the ratios of heart weight to body weight do not differ significantly from normals established by Herrmann.[11] Eyster stated, however, that they differed from values for 17 normals observed in his laboratory. Data were not supplied. Doubt exists that distinct hypertrophy was achieved in this group of dogs and proof of dilatation followed by hypertrophy is supported in only one instance.

Later, Eyster[2] reported that if the rubber tie on the aorta were removed after 3 to 6 days the hearts of these animals hypertrophied comparably to those with the tie intact. The number of animals used was not indicated, the measurements of the x-ray silhouettes were not given, and no heart weights were recorded. X-ray pictures of one dog were published. It was stated that if dogs were sacrificed soon after producing experimental aortic insufficiency, aortic stenosis, or interventricular septal defects, changes in the heart muscle could be demonstrated. Microscopic examination of the left ventricular heart muscle showed "hydropic degeneration." No illustrations were shown. It is not clear how many of the dogs in the aortic stenosis group were thus examined.

To add more support to the theory, massive blood transfusions were given to another set of dogs.[9] A graph of the area of the x-ray silhouette of two of these dogs was recorded. The graph showed significant enlargement of the cardiac areas in these two animals several weeks after the initial transfusion and further enlargement after a second transfusion. Transitory increase in the cardiac area followed each transfusion and then a decrease in cardiac shadow occurred before the development of persistent enlargement. Terminal heart weights were not published. Although full documentation is lacking, there appears to be no obvious error in this ancillary experiment.

OTHER EXPERIMENTS

The latter facet of Eyster's work was the first to be questioned. Herrmann and Decherd[12] in 1939, gave massive transfusions of acacia solutions to 100 rabbits and 40 white rats. No significant increase in heart weight/body weight was detected.

In 1945, Beznák and Hajdu[13] tested the Eyster theory, using white rats. Silver rings of standard diameter were placed to constrict the ascending aorta in 82 male rats of standard weight. After 2 days the rings were removed from 26 animals. Thirteen of these animals were killed 7 days after removal of the rings, and 13 were sacrificed 28 days after removal of the rings. No increase in average heart weight occurred. In no single animal with the constriction removed was the heart weight greater than normal. The rings were left in place in 56 animals. After 7 days with the rings in place, 43 rats had an average increase of 14 per cent in heart weight, and 13 rats with the rings in place for 28 days showed an average increase of 29 per cent in heart weight.

In a recent study rats were exposed to brief sudden atmospheric decompression by Stickney, Northrup, and Van Liere.[14] The procedure produces immediate dilatation of the heart by release of gases in the blood stream[15] and is accompanied, at times, with myocardial damage.[15,16] Ten of 11 rats had a significant (18 per cent) increase in the heart's x-ray shadow immediately after exposure to low atmospheric pressure. None had an increased heart weight-body weight ratio when sacrificed 6 weeks after exposure. Thirty-two other rats were exposed frequently to the low atmospheric chamber and in none was the weight of the heart increased.

CLINICAL EVIDENCE

Many exceptions to the concept of dilatation and injury causing cardiac hypertrophy are noted in clinical medicine. In the more striking examples the heart enlarges rapidly and returns quickly to normal size without developing hypertrophy. In many of these, pathologic changes in the muscle fibers of a degree more severe than hydropic degeneration have been demonstrated. Documented instances of this sequence are noted in diphtheria,[17,18] acute rheumatic fever,[19,20] acute pulmonary embolism,[21] acute glomerulonephritis,[22] and postpartum heart disease.[23] With suitable therapy for anemia,[24,25] beriberi,[26,27] hypertension,[28,29] and arteriovenous aneurysm,[30] heart size frequently returns quickly to normal without subsequent enlargement.

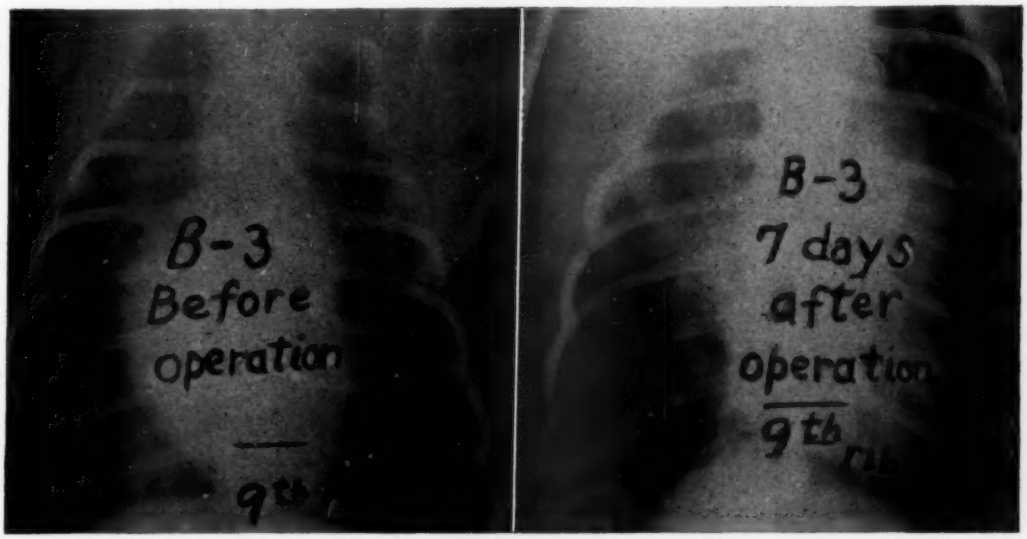


Fig. 1.—Alterations of dog's frontal cardiac silhouette before placing an aortic constriction, and seven days after the constriction has remained in place. Marked distortion of the frontal area of the heart's projection is evident. The difference is greater than would be expected with changes of the cardiac or respiratory cycle, or secondary to aortic constriction. Mediastinal shift is apparent.

EXPERIMENTAL METHODS

Similar to Eyster's experiments, a rubber tie was placed about the proximal aorta of randomly selected mongrel dogs during open-chest operations. The tie was tightened until a distinct thrill was felt. The dogs were divided without bias

into two groups. In the first group (A) the tie was removed after 5 days at a second operation. In Eyster's experiment the tie was removed at the height of dilatation, as determined by the heart's x-ray shadow. Eyster stated this was usually between the third and sixth postoperative days. Despite care in positioning the animal and attention to its phase of respiration, x-ray mensuration was not a reliable index of heart size in the present study. Shift of the mediastinum following operation often caused marked distortion of the frontal cardiac shadow, as illustrated in Fig. 1. Because of this difficulty the fifth day was chosen arbitrarily for removal of the tie in our dogs of the first group. In the other group (B) the rubber tie was left in place until the conclusion of the experiment.

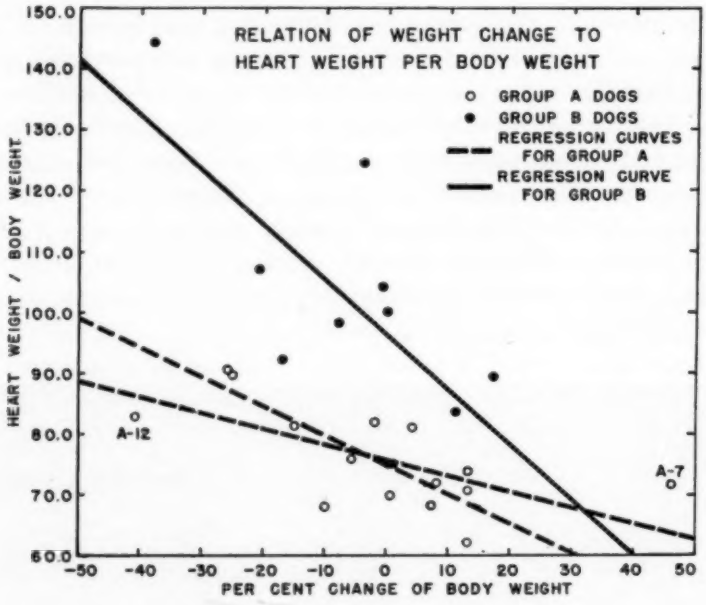


Fig. 2.

Between 29 and 156 days after operation the animals were sacrificed, except for 2 dogs of group B whose aortas ruptured earlier at 11 and 15 days, respectively. The hearts were washed free of clots and weighed (±0.10 gram). Casts of the ascending aortas were made with Wood's metal to visualize the aortic constriction. Measurements of the cross-sectional area of the aortic lumen at the site of the tie and of unconstricted aorta proximal to the tie were obtained. Pliable wire was molded about the models at these sites and removed in two sections. These were employed to obtain the cross-sectional outlines of the aortic segments, and their areas were determined graphically. Sections of left ventricle were examined microscopically to estimate muscle fiber size. To indicate whether edema of the ventricular muscle contributed to the weight of the heart, ash contents were determined on a few samples of left ventricle.

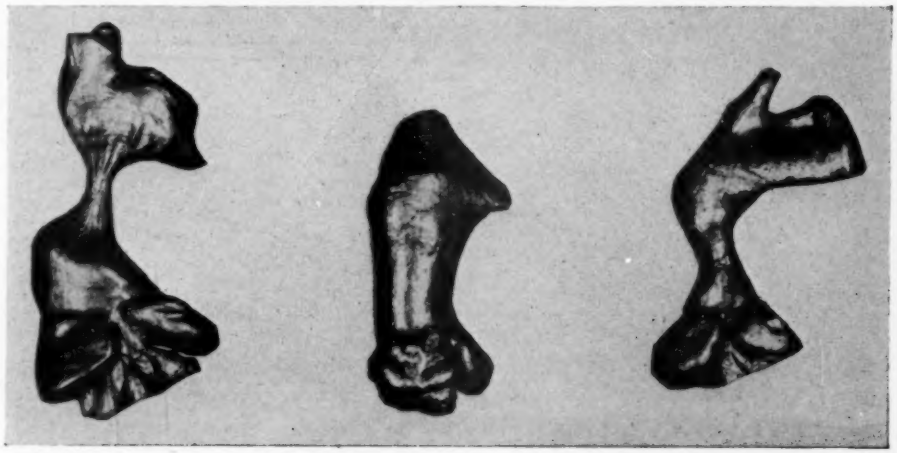
RESULTS

Seventy operations were performed on 50 dogs. Fifteen died at operation; 10 died within 10 days, 7 from aortic rupture and 3 from pulmonary edema.

The tie was removed from 15 animals after 5 days. In 10 animals the tie was left in place until sacrifice.

The mean heart weight-body weight ratio of the 15 dogs with the tie removed was 75.9* (Table I). This ratio does not differ from that for normal mongrel dogs (79.8),[11] (75.5).[31] The range of the ratio for the 15 dogs was 62.2 to 90.6; clearly within the range for normals (53.5 to 99.4).[11,31]

The mean heart weight-body weight ratio for 10 dogs with the tie left in place was 101.8 (Table II). This ratio is significantly different ($t = 4.4$, $p < 0.001$) from that of the 15 dogs with ties removed. The ratio is also clearly different from previously established means for normal dogs, and lies slightly outside the given range for most normals.



B 7 *A 7* *B 12*

Fig. 3.—Wood's metal casts of the ascending aorta of dogs with a constricting tie left in place (B 7, B 12) and with the tie removed after five days (A 7).

Weight change was common following operation (Fig. 2). For dogs in both groups a significant correlation ($r = -.647$, $r = -.715$) was noted for change in heart weight-body weight ratio related to change in weight. When regression curves were constructed and submitted to the statistical method of analysis of variance, so that the influence of weight change was accounted for in each group, there remained a highly significant difference between the heart weight-body weight ratios of the two groups ($F = 32.57$, $p > 0.001$). The slope of the two regression curves is slightly different ($F = 5.93$, $p > 0.05$). If the two animals whose weight changed the greatest amount are omitted from the group with aortic ties removed, the slopes of the regression curves are not different, and the difference between the mean heart weight-body weight ratio remains at the same high level of significance ($F = 30.62$, $p > 0.001$).

Casts of the aortas indicated no significant constriction in the group with the ties removed (Fig. 3). In the other group, with the ties left in place, there was judged to be significant constriction, varying from 42 per cent reduction of the area of the aortic lumen to total obstruction (Tables I and II). On 3 specimens

*This ratio for convenience is expressed in the text and table as 10^{-4}.

TABLE I. DOGS WITH AORTIC TIE REMOVED AFTER FIVE DAYS

DOG NO.	SEX	BODY WEIGHT (KG.)		CHANGE IN BODY WEIGHT PER CENT	HEART WEIGHT (GRAMS)	HEART WEIGHT / BODY WEIGHT (10^{-4})	AREA OF AORTIC LUMEN (SQ. MM.)			DURATION OF EXPERIMENT (DAYS)
		INITIAL	SACRIFICE				PROXIMAL TO TIE	AT SITE OF TIE	PER CENT CHANGE	
A–4	M	9.1	10.3	+13	72.8	70.6	29.0	29.0	0	110
A–5	F	9.2	10.4	+13	76.7	73.6	43.5	43.5	0	156
A–6	M	7.9	8.9	+13	55.3	62.2	21.6	21.6	0	147
A–7	M	8.9	13.0	+46	93.1	71.6	54.7	42.0	−23	119
A–8	M	10.5	10.9	+ 4	88.4	81.0	25.2	25.2	0	105
A–11	F	12.0	8.7	−26	78.8	90.6	19.3	19.3	0	119
A–12	F	9.3	5.5	−41	45.5	82.8	21.0	21.0	0	113
A–13	F	11.6	10.4	−10	70.8	68.0	11.3	11.3	0	48
A–16	M	7.2	6.8	− 6	51.4	75.8	25.8	25.8	0	42
A–18	M	8.7	8.5	− 2	69.9	82.4	38.7	30.6	−21	35
A–27	M	13.3	13.4	+ 1	93.6	69.6	42.0	37.1	−12	53
A–28	M	8.3	8.9	+ 7	61.7	68.2	25.8	25.2	− 6	52
A–29	M	10.4	7.8	−25	70.0	89.7	38.2	38.2	0	28
A–32	M	8.4	9.1	+ 8	65.3	71.9	35.3	35.3	0	43
A–36	M	10.3	8.7	−15	70.4	81.2	60.2	48.4	−19	29
Means			9.4		70.9	75.9				

TABLE II. DOGS WITH AORTIC TIE LEFT IN PLACE

DOG NO.	SEX	BODY WEIGHT (KG.)		CHANGE IN BODY WEIGHT PER CENT	HEART WEIGHT (GRAMS)	HEART WEIGHT / BODY WEIGHT (10^{-4})	AREA OF AORTIC LUMEN (SQ. MM.)			DURATION OF EXPERIMENT (DAYS)
		INITIAL	SACRIFICE				PROXIMAL TO TIE	AT SITE OF TIE	PER CENT CHANGE	
B–4	M	8.9	9.0	+ 1	67.7	75.2	29.0	8.3	−71	82
B–7	M	9.1	5.6	−38	81.0	144.5	64.5	16.1	−75	26
B–8	F	13.5	15.2	+11	125.6	83.7	54.9	11.3	−80	135
B–12	F	7.6	7.5	− 1	78.6	104.0	33.9	12.9	−62	105
B–13	F	4.8	4.0	−17	36.8	92.1	17.7	9.7	−42	93
B–14	F	6.0	5.5	− 8	54.0	98.2	Ruptured aorta			91
B–30	M	10.4	10.4	0	104.0	100.0	Ruptured aorta			15
B–31	F	7.5	9.0	+17	80.2	89.3	42.0	9.7	−77	31
B–33	M	7.7	6.1	−21	65.3	107.0	53.2	6.4	−87	30
B–34	M	10.9	10.2	− 4	127.0	124.0	Ruptured aorta			11
Means			8.2		82.0	101.8				

the narrowing of the vessel was complete. In these rupture had occurred proximal to the site of the aortic tie.

The dry weight of the heart samples did not differ from normal values. Microscopic examination of sections of the left ventricles disclosed no abnormalities.

DISCUSSION

The present study, in conformity with clinical observations and in agreement with other experiments cited, fails to confirm the theory that injury accompanying dilatation of the heart causes persistent hypertrophy. Experimental results appear the same whether rabbits, rats, or dogs are used.

The criterion used by Eyster for hypertrophy of the canine heart—x-ray mensuration—was not reliable in our study. The technique has also been criticized by Drury.[32] Terminal heart weight-body weight ratios, which represent our choice for hypertrophy criterion, were not published with Eyster's experiments.

It is to be noted in our experiment recorded above that actual proof of cardiac dilatation is wanting. It was demonstrated in the study of Stickney, Northrup, and Van Liere.[14] It was reasonably inferred, more than proved, in the original experiments regarding the theory. In repeating the experiments it was assumed that if dilatation and myocardial injury were produced in the original experiments, comparable changes were produced in the present one. Support for the adequacy of the aortic constriction in the present study is found in the development of hypertrophy in the animals with the tie left in place. This hypertrophy is more distinct than was reported in the original experiments. It seems likely that any myocardial changes subsequent to aortic constriction produced in Eyster's experiments also occurred in the present study.

The influence of weight change on the heart weight-body weight ratio is of interest (Fig. 2). The direction of change is as expected but is not well documented in the literature.[31,33-37] Perhaps if a greater range of weight changes were included, the expression of the ratio would not remain linear. While the correlation expressing this influence is not as close as that for heart weight/body weight alone ($r = +.915$), it is large enough to demand correction in experiments accompanied by weight change.

The dry weight determinations of the ventricular musculature, although not conclusive,[38] imply, as have similar experiments,[13] that the increase in heart weight was not caused by fluid retention. Animals with evidence of heart failure were excluded. The absence of microscopic evidence of hypertrophy was not unexpected. The amount of hypertrophy produced was slight. Moderate hypertrophy is required before it is apparent with the microscope.[35,39]

SUMMARY

Experimental and clinical evidence contrary to the theory of injury of the heart accompanying dilatation as a cause of cardiac hypertrophy is cited. Results from repetition and extension of the basic experiments from which the theory was launched fail to support the theory. No instance of cardiac hypertrophy was found in 15 dogs after a constricting tie was removed from the aorta after 5 days. In 10 other dogs with the aortic tie left in place from 11 to 135 days,

a significant increase in the heart weight-body weight ratio compared to normal was demonstrated. A significant relation between body weight change and heart weight-body weight ratio was noted in the experimental animals.

CONCLUSION

Evidence does not support the theory of cardiac dilatation and myocardial injury in causing hypertrophy of the heart.

I wish to thank Dr. Jesse Wofford for help with the surgical technique, and Dr. M. A. Brumbaugh, and Miss Geraldine Fellers of the Bristol Laboratories for help and expert advice in the statistical analysis.

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OBSTRUCTIVE AND RELATIVE AORTIC STENOSIS. DIFFERENTIAL DIAGNOSIS BY PHONOCARDIOGRAPHY

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THE diagnosis of aortic stenosis has considerable importance, not only in regard to the prognosis, but also in view of a possible correction of the valvular deformity. It has been known for a long time that a systolic murmur over the second right intercostal space may be caused by either narrowing of the aortic valve (organic aortic stenosis) or dilatation of the ascending aorta (relative stenosis). Minimal narrowing due to fibrosis or calcification of the leaflets may also cause a loud murmur even though no obstruction results from the process.

Evaluation of the stenosis can be obtained through left heart and aortic catheterization or, more approximately, by the study of the carotid tracing and the aortic electrokymogram.

This study was undertaken with the purpose of ascertaining whether phonocardiography can be used in the differential diagnosis between organic and relative stenosis, and between obstructive and nonobstructive lesions of the aortic valve.

PREVIOUS STUDIES

Phonocardiography.—Graphic studies of the cardiac murmurs have been done in cases with aortic stenosis for the last 20 years. It is recognized that the typical murmur of aortic stenosis has usually a rhomboid shape and that its upper line resembles the curve of a pulse wave.[1-8] This murmur subsequently has been called "diamond shaped," a term which has become popular even though it is not always accurate. The murmur frequently lasts until the second sound. Furthermore, it has been noted that the aortic component of the second sound may be extremely small and delayed, and that this can be best ascertained by recording the tracing in the first right intercostal space, where the pulmonic component is less evident. Cases with congenital (probably subaortic) stenosis present a rather early peak of the "diamond."[9] It was noted in 1948,[3] that the murmur of aortic stenosis may be an all-systolic murmur obscuring the second sound; and it was suggested to record the tracing in 3 areas: in the second right intercostal

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space, in the suprasternal notch, and on the right carotid artery. The 3 tracings revealed a typical murmur in cases with obstructive stenosis. Still, phonocardiography did not seem able to differentiate between the murmur of moderate obstructive stenosis, that caused by nonobstructive fibrosis of the aortic valve, and that caused by dilatation of the ascending aorta.

Sphygmography—Electrokymography.—A typical modification of the pulse tracing was reported in 1896[11,12]; it consisted of a slow rise and a notch in the ascending branch of the pulse (*anacrotic notch*). Subsequent studies confirmed this finding.[13-16] It was suggested[3] to record the pulse at the suprasternal notch, where no pressure is exerted on the pulsating vessels (aorta), and over the right carotid and right subclavian arteries. It has been shown[17] that carotid tracings are more revealing than brachial or tibial pulse tracings. The carotid tracing should be taken without strong compression of the artery, so as not to narrow the artery and cause an abnormal contour. A cuff wrapped around the neck and inflated at 20 mm. Hg may be used for such purpose.[17]

The slow rise of the pulse was also found in the electrokymogram of the aortic arch.[8]

MATERIAL AND METHOD

Our graphic survey was made on the records of 70 cases studied in the Division of Cardiology. The various clinical, roentgenologic and electrocardiographic data indicated organic, obstructive stenosis in 30 cases. The other 40 cases had either nonobstructive fibrosis of the aortic valve or a relative stenosis (dilatation of the aorta).

The diagnosis of obstructive stenosis was confirmed in 5 cases by surgery[3] or autopsy.[2] As the diagnosis of obstructive stenosis was either confirmed or excluded in several cases by pulse tracings, a brief summary of the relevant data is indicated. All cases were studied by means of electrocardiography and phonocardiography. The phonocardiographic tracing was recorded over 5 areas of the precordium, according to a routine method of investigation.[8] The "stethoscopic" and "logarithmic" tracings were used until 1954, in conjunction with either a Sanborn Stetho-Cardiette or a Twin-Beam apparatus. Since 1954, selective bands of frequency also have been recorded,[19] usually in the ranges 60-110 and 150-200 per second.

TABLE I. AGE OF PATIENTS STUDIED

AGE (YEARS)	ORGANIC STENOSIS	RELATIVE STENOSIS
10–20	6	—
21–30	6	—
31–40	6	2
41–50	8	6
51–60	3	13
61–70	1	12
71–80	—	7
Total No.	30	40

TABLE II. AMPLITUDE OF THE MURMUR

	ORGANIC STENOSIS	RELATIVE STENOSIS
Large	8 = 26.7%	8 = 20%
Medium	9 = 30%	12 = 30%
Small	13 = 43.3%	20 = 50%
Total number of cases	30	40

TABLE III. SHAPE OF THE MURMUR

	ORGANIC STENOSIS	RELATIVE STENOSIS
Early diamond	4 = 13.3%	35 = 87.5%
Middle diamond	6 = 20%	3 = 7.5%
Late diamond	20 = 66.7%	2 = 5%
Total number of cases	30	40

TABLE IV. PHASE OF THE MURMUR

	ORGANIC STENOSIS (NUMBER OF CASES)	RELATIVE STENOSIS (NUMBER OF CASES)
Beginning of murmur after first sound	16 cases (53.5%) = 0.04-0.05 sec.	4 cases (10%) = 0.03-0.04 sec.
	14 cases (46.7%) = immediately	36 cases (90%) = immediately
End of murmur before second sound	13 cases (43.3%) = 0.04-0.07 sec.	37 cases (92.5%) = 0.04-0.08 sec.
	17 cases (56.7%) near second sound	3 cases (7.5%) near second sound

TABLE V. AMPLITUDE OF THE SECOND AORTIC SOUND

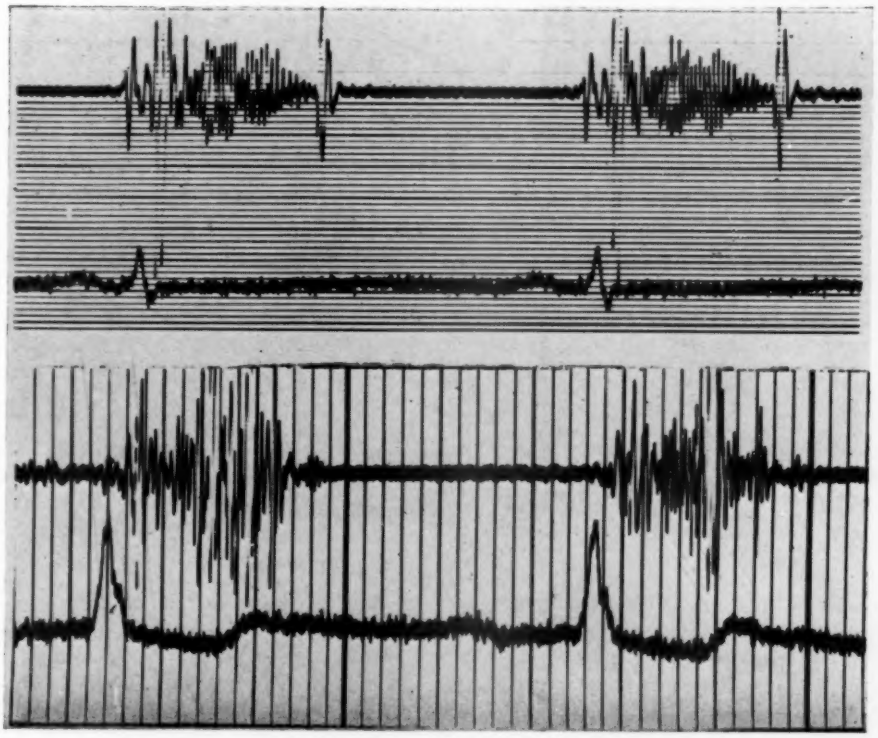
AMPLITUDE OF A_2	ORGANIC STENOSIS	RELATIVE STENOSIS
Small	11 = 38.7%	11 = 27.7%
Medium	10 = 33.3%	12 = 30%
Large	9 = 28%	17 = 42.3%
Total number of cases	30	40

The tracing of the suprasternal notch was studied in 32 cases by means of a 1.5 inch funnel and a crystal microphone of a "linear" type.

Carotid sphygmograms were recorded in 36 cases by means of the same microphone connected with either a small funnel (held by hand) or a blood-pressure cuff wrapped around the neck and inflated at 20 mm. Hg. The electrokymogram of the aortic arch was recorded in 11 cases.

The ages of the patients are presented in Table I.

A.



B.

Fig. 1.—Phonocardiograms recorded with a "stethoscopic" method over the second right intercostal space. (*A*) Relative stenosis (aortitis), early diamond-shaped murmur. (*B*) Organic stenosis (rheumatic), late diamond-shaped murmur.

RESULTS

1. *Amplitude of the Murmur.*—The amplitude of the murmur was arbitrarily evaluated as large, medium, or small by comparing the height of the vibrations with that of the first sound. *Large* was equivalent to or greater than the first sound. *Small* was equivalent to or smaller than one-half of the first sound. *Medium* was intermediate between the two. Table II shows the amplitudes of the murmurs. No statistically significant difference was found by comparing cases with organic stenosis and those with relative stenosis.

2. *Shape of the Murmur.*—The point of maximum intensity of the murmur was noted, and its position in regard to the first and second sounds was ascer-

tained. *Early diamond-shaped murmur* was defined as one where the peak of the murmur was before one-half of the distance between the largest vibration of the first sound and the largest vibration of the second. *Late diamond-shaped murmur* was defined as one where the peak of the murmur was after one-half of this distance. *Middle diamond-shaped murmur* was termed as one where the peak was at about one-half of this distance.

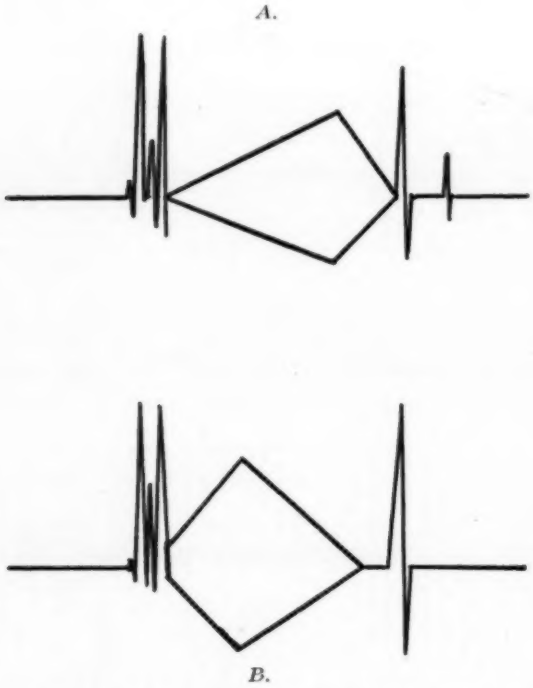


Fig. 2.—Scheme of systolic aortic murmurs. (*A*) Late diamond, typical of an organic, obstructive lesion of the aortic valve. (*B*) Early diamond, typical of relative stenosis.

Table III shows the results of this study. Cases with organic stenosis had a predominance of late and middle diamond-shaped murmurs, while cases with relative stenosis had an extreme majority of early diamond-shaped murmurs and a small minority of the others (Figs. 1 and 2). The late-diamond type of murmur is even better revealed by selective phonocardiography (Fig. 3,*A*).

3. *Phase of the Murmur.*—A special study was made in order to ascertain how soon the murmur did start after the main vibration of the first sound and how near it was to the main vibration of the second sound. Table IV shows the results. While only about one-half of the murmurs caused by organic stenosis started immediately after the first sound, 90 per cent of those caused by relative stenosis did so. While only about one-half of the murmurs caused by organic stenosis terminated at some distance from the second sound, over 90 per cent of those caused by relative stenosis did so. Thus, early beginning and early ending is more typical of relative stenosis than of organic stenosis. It should be noted, however, that in a few cases of organic stenosis the murmur had a roughly triangular shape and terminated abruptly, long before the second sound.

In certain cases, it was noted that the shape of the murmur varied from cycle to cycle in an alternating way. The alternation consisted in such a variation of shape that one cycle had an early-diamond shape while the next had a late-diamond shape, and so on.

In combined lesions (organic stenosis plus insufficiency) the systolic murmur usually terminated before the second sound; in cases with severe insufficiency the systolic murmur was either a middle or early diamond (occasionally it was difficult to differentiate it from that of relative stenosis).

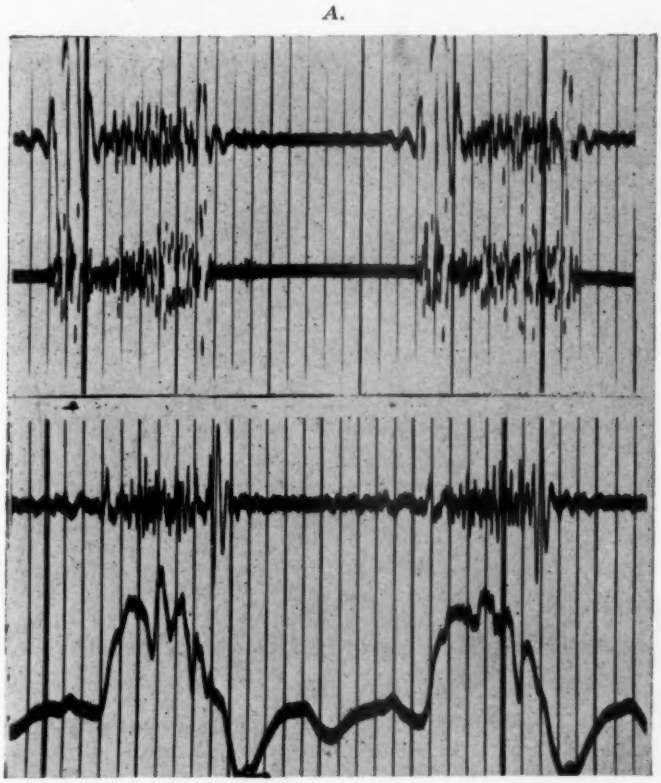


Fig. 3.—(*A*) Aortic systolic murmur in a case of organic aortic stenosis; above, "stethoscopic" tracing; below, selectively filtered tracing (60-110) better revealing the late-diamond shape of the murmur. The tiny vibration which follows the large second pulmonic component is the aortic component of the second sound. (*B*) Organic aortic stenosis; above, stethoscopic tracing over third left intercostal space; below, low-frequency tracing at the suprasternal notch (aortic pulse).

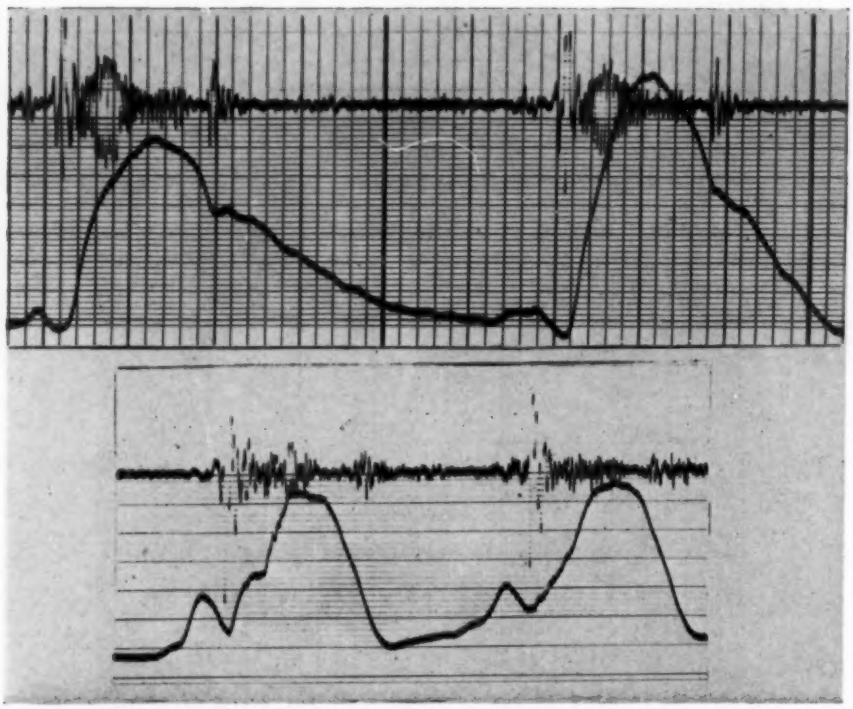
4 *Amplitude of the Second Aortic Sound.*—Diagnostic importance has been attribtued to a weakening of the second sound. We considered the sound as large if it was three-fourths or more than the first sound; as small if it was one-half or less than the first sound; as intermediate when it was between one-half and three-fourths of the first sound.

In many cases of organic stenosis, the aortic component was revealed by a tiny vibration which followed the pulmonic component by 0.07 to 0.09 second (Fig. 3,*A*). It is possible that in some of the cases where the second sound seemed large we were actually considering the pulmonic and not the aortic

component while the latter was not visible. The results of the study are presented in Table V.

Large, medium, and small sounds were found in both groups. However, a large sound was more frequent in relative stenosis (42.3 per cent versus 28 per cent); a small sound, in organic stenosis (38.7 per cent versus 27.7 per cent).

A.



B.

Fig. 4.—Sound tracings and carotid tracings. (*A*) Relative stenosis (aortitis), early diamond in the aortic phonocardiogram. (*B*) Obstructive stenosis, sound tracing of the carotid artery; slowly rising pulse; vibrations in the ascending branch (first pulse).

5. *Tracing of the Suprasternal Notch, Aortic Electrokymogram and Carotid Tracing.*—The following were noted:

A. *Organic stenosis:* Ninety-one per cent of the cases presented a pulse tracing with typical characteristics (Figs. 4,*B*, and 5): slow rise, anacrotic notch, and plateau with multiple vibrations. Occasionally, the anacrotic notch which was present in the suprasternal tracing was not visible in the carotid tracing.

B. *Relative stenosis:* Eighty-two per cent of the cases presented a pulse with a rapid rise, no anacrotic notch, and no multiple vibrations. Roughly, one fourth had a rounded appearance without vibration or anacrotic notch (Fig. 4, *A*). Eighteen per cent had a rather slow rise and a small anacrotic notch, but few uncharacteristic vibrations.

It was also noted that the rapidity of rise of the pulse was significant. In 67.5 per cent of the cases with organic stenosis, the distance between beginning of the

first sound and peak of the carotid pulse was between 0.12 and 0.14 second (occasionally more). In 64 per cent of the cases with relative stenosis, the distance between the beginning of the first sound and the peak was between 0.07 and 0.08 second (occasionally less). This measurement may be difficult if the pulse has a rounded top.

6. *Electrokymogram of Aortic Arch.*—The tracings are similar to those of the carotid sphygmograms (Fig. 5). In organic stenosis it is typical to find a slow rise, an anacrotic drop, or a jagged contour. Frequently, the pulsation is small and requires considerable amplification. In relative stenosis a tall, rapid, peaked or rounded pulsation is the rule.

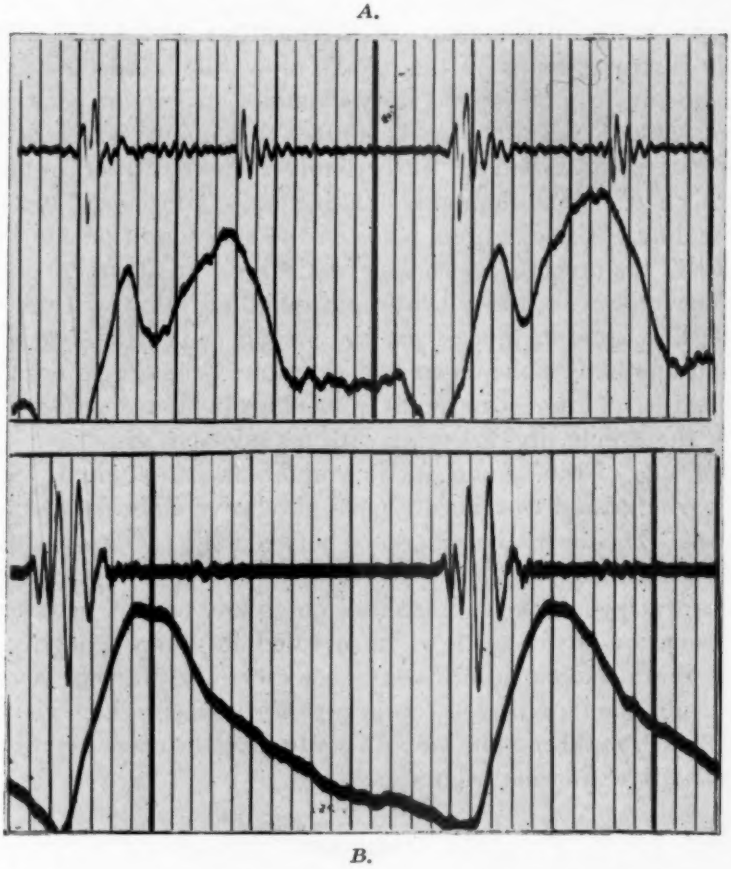


Fig. 5.—Electrokymograms of the aortic arch in cases with basal systolic murmurs (the sound tracings were recorded at the apex). (*A*) Obstructive calcific aortic stenosis. Aortic pulse with sharp notching and late peak. (*B*) Atherosclerosis of aorta. Normal aortic pulse.

DISCUSSION

This study was made in 70 clinical cases. In the great majority of them, the history, the physical and roentgenologic data, and the clinical course permitted a clear-cut division between those who had an organic, obstructive narrowing of the aortic valve and those having a systolic murmur due to relative stenosis or to minor, nonobstructive processes affecting the aortic wall or the aortic

leaflets. Moreover, the diagnosis of obstructive stenosis was confirmed in 5 cases by either surgery or autopsy.

It was more difficult to decide whether an organic lesion was aortic or subaortic, even though physical data are claimed to be significant (lower point of maximal intensity of the murmur, louder second aortic sound in subaortic stenosis).

No statistically significant difference was found in the graphic study of the amplitude of the murmur between organic and relative stenosis. This confirms a known clinical fact, namely, that cases with relative stenosis may have a loud systolic murmur, while cases with severe obstruction of the aortic valve may have only a moderately loud murmur.

The graphic study of the shape of the murmur revealed significant differences between the two groups; if the middle of systole is selected as a point of division, the murmur can be called "early diamond" when the peak is before this point, "late diamond" when the peak is after this point. Over 87 per cent of cases with relative stenosis had an "early diamond," over 66 per cent of cases with organic stenosis had a "late diamond." This may be considered as a useful point in the graphic differential diagnosis between the two conditions.

The phase of the murmur was also investigated. In about 90 per cent of the cases with relative stenosis, the murmur started immediately after the first sound and terminated at some distance from the second sound (0.04 to 0.08 second), while less than one half of the cases had the same behavior in organic stenosis. Even though this is an interesting point, it can hardly have diagnostic significance on account of the evenly divided cases with organic stenosis.

The amplitude of the second aortic sound was also studied. It was noted that a large second sound was more typical of relative stenosis; a small sound, of organic stenosis. However, the difference between the two groups did not seem to have clinical significance.

The pulse tracings of the suprasternal notch and carotid arteries, as well as the electrokymogram of the aortic arch, revealed data of diagnostic significance. In particular, the mechanical and roentgenologic pulse tracings revealed a slow rise and a flat, notched, or jagged top in organic stenosis which contrasted with the large pulse with rapid rise and smooth contour of the cases with relative stenosis or nonobstructive, minimal stenosis.

SUMMARY

Seventy clinical cases with loud aortic systolic murmurs were investigated by clinical, roentgenologic, and graphic means.

The tracing of the suprasternal notch, the carotid tracing, and the aortic kymogram presented data (slow rise, flat top, or anacrotic notch, multiple vibrations) which were helpful in the differential diagnosis between obstructive stenosis, minor nonobstructive aortic lesions, and relative aortic stenosis.

The phonocardiogram revealed that no statistical significance could be attached to the amplitude of the murmur and its distance from the first and second sound, or to the magnitude of the second aortic sound. The shape of the murmur, on the contrary, seemed important since 87.5 per cent of the cases with relative

stenosis had an "early diamond" and 66.7 per cent of the cases with organic stenosis had a "late diamond." A late beginning and a late termination of the murmur, and a small, delayed second aortic sound are found more often in organic, obstructive valvular stenosis than in relative or nonobstructive stenosis.

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HEMORRHAGIC PERICARDITIS, PLEURISY, AND PNEUMONIA COMPLICATING RECENT MYOCARDIAL INFARCTION

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IN THE past few years, hemorrhagic pericarditis (hemopericardium) has been reported as a complication of acute myocardial infarction and anticoagulant therapy as etiological factor was discussed.[1-6] The present report deals with three instances of recent myocardial infarction complicated by intensely hemorrhagic pericarditis, pleurisy, and pneumonia, respectively. Experience derived from these cases and others reported in the literature[4,7,8] indicates the necessity to reconsider the etiological factors responsible for hemorrhagic complications of myocardial infarction.

CASE REPORTS

1. *Hemorrhagic Pericarditis.*—

Case 1.—N. G., a 59-year-old man, was admitted to the hospital because of chest pain aggravated by breathing and symptoms of congestive heart failure. In August 1954, while driving his car, the patient experienced severe pain across his chest and in both arms which lasted for about 4 hours. Subsequently, typical angina of effort developed. An attack similar to that of August 1954, but milder and of shorter duration occurred in March 1955. The severest attack was on March 9, 1956. The pain was excruciating and the patient gasped for breath. An electrocardiogram indicated recent posterior wall infarction. The patient rested at home for 4 weeks. About April 1956, a new type of pain developed which, unlike the previous one, was not relieved by nitroglycerin. It was localized in the lower half of the sternum and the left side of the neck; it was aggravated by deep inspiration and relieved by assuming upright posture. No temperature readings were taken at that time. X-ray study revealed "enlargement of the heart." Dyspnea and signs of congestive heart failure developed and were little influenced by digitalis and diuretics. The pain in the chest and neck improved for a while but recurred. The patient was admitted to the Maimonides Hospital on May 26, 1956.

Physical examination at this time revealed a rectal temperature or 101.6° F., blood pressure of 124/80 mm. Hg, and a heart rate of 84 per minute. The patient was apparently not in acute distress, but slight effort caused shortness of breath. There was no pitting edema. Homans' sign was negative. The lungs were clear. The apex beat of the heart was not palpable. The cardiac dullness was bilaterally enlarged. Complete flatness to percussion of the lower half of the sternum suggested pericardial effusion. A Grade 2 blowing systolic murmur was heard in the apical area. The heart sounds were faint over the base of the heart and the second pulmonic sound was louder than the aortic sound. The hepatic region was tender to palpation.

Laboratory findings: On May 28, 1956: hemoglobin 14 Gm./100 ml.; leukocytes 5,750 per c. mm. with 62 per cent neutrophils; sedimentation rate 38 mm./hr. (Wintrobe); urine and blood chemistry normal. On May 30, the venous pressure was 190 mm. H_2O, rising to 300 mm. on pressure upon the right upper abdominal quadrant. On May 31, leukocytes 7,600 per c. mm. with 79 per cent neutrophils. The electrocardiogram showed signs of posterior wall infarction

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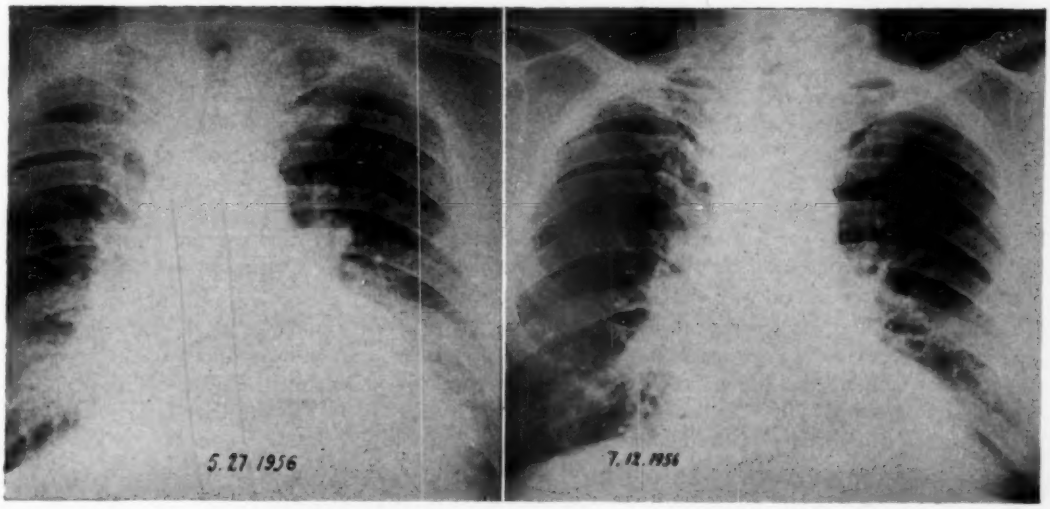
and digitalis effect. X-ray study of the chest (Fig. 1,*A*) on May 27, 1956, revealed "enlargement of the heart mainly to the left, but also to the right, widening of the cardiac waist and marked pulmonary congestion."

Course: For the first 5 days the temperature ranged from 101° to 101.8° F. A pericardial friction rub was heard on May 28 and 30. The cardiac dullness increased and dyspnea became more marked. Pericardial paracentesis was performed on May 31. About 30 c.c. of intensely hemorrhagic fluid were withdrawn. Culture of the aspiration fluid as well as blood cultures remained sterile. On June 1, the temperature fell to normal. Although only a small quantity of pericardial fluid was withdrawn, rapid improvement followed. Within 24 hours of the paracentesis the patient claimed he "felt wonderful." On June 4, the cardiac dullness was diminished. X-ray study (Fig. 1,*B*) on July 12, 1956, revealed decrease of the transverse diameter of the heart waist and "marked reduction in the right cardiac distance." Increased diuresis resulted in a loss of 10 pounds of body weight within 10 days. The heart rate fell to 64 per minute. Tenderness in the hepatic region disappeared. A tuberculin skin test was negative. The patient was discharged on June 12, 1956. At no time had he received anticoagulant treatment.



A. *B.*

Fig. 1.—Case 1. The films taken at an interval of 6 weeks show first, enlargement, and then reduction in the size of the cardiac silhouette.

Within 5 weeks of discharge the patient developed 2 attacks of urticaria, the first following an injection of a mercurial diuretic, the second occurring without apparent cause. The attacks subsided upon administration of cortisone. The patient was then free of complaints and was able to return to full employment 9 weeks after admission to the hospital, that is, 5 months after the onset of myocardial infarction.

Summary: Six weeks following myocardial infarction, pain of the pericardial type and congestive heart failure developed. Eleven weeks after onset of the coronary infarction, symptoms and signs of pericardial effusion were noted. Pericardial paracentesis revealed intensely bloody fluid. Cultures of blood and aspiration fluid yielded no growth. The patient had not received anticoagulant treatment.

2. *Hemorrhagic Pleurisy.*—

Case 2.—S. S., a 54-year-old man, was admitted on Jan. 22, 1955. While shoveling snow on that day the patient experienced severe substernal pain accompanied by cold perspiration.

An electrocardiogram showed deep Q deflections and elevated S-T segments in Leads II, III, aV_F and V_6, suggestive of posterolateral wall infarction.

On admission the rectal temperature was 98.4° F.; blood pressure 140/90 mm. Hg; heart rate 90 per minute. Homans' sign was negative. There was no evidence of congestive heart failure. The lungs were clear. The heart dullness was not abnormally increased. The heart sounds were fair in the apical area, and rather faint at the base of the heart. The heart action was regular.

Laboratory findings: On Jan. 26, 1955: urine negative; fasting blood sugar 146 mg. per cent; hemoglobin 12.8 Gm. per cent; red blood cells 3,750,000 per c. mm.; leukocytes 11,100 per c. mm. with normal differential count; sedimentation rate 25 mm. per hour.

Course: On the second day of illness the temperature rose to 102.2° F. The patient felt pain at the left of the sternum, aggravated by breathing and cough. Pericarditis was suspected. The electrocardiogram showed, besides the changes noted previously, elevation of the S-T segment in all precordial and standard limb leads. It was noted that elevation of S-T in Lead aV_F was not accompanied by reciprocal depression in aV_L. These signs lent support to the diagnosis of pericarditis.

On the fifth day of illness the patient complained of pain in the precordial area. A loud pericardial friction rub was noticed on the sixth day and remained audible over a wide area for 10 days. The temperature was elevated for 8 days, with peaks of from 101° to 102° F., and then decreased. However, on the twelfth day of illness, it climbed again simultaneously with the appearance of stabbing pain in the left hemithorax. Dullness and diminished vocal fremitus were noticed over the base of the left lung. At no time was there evidence of thrombophlebitis nor did the patient expectorate bloody sputum.

On the fourteenth day of illness (February 4), x-ray study of the chest (Fig. 2,*A*) revealed enlargement of the cardiac silhouette and pulmonary congestion. The cardiac border and the diaphragm were obscured on the left side by a pleural effusion. There was evidence, also, of effusion along the lateral wall of the right side of the chest.

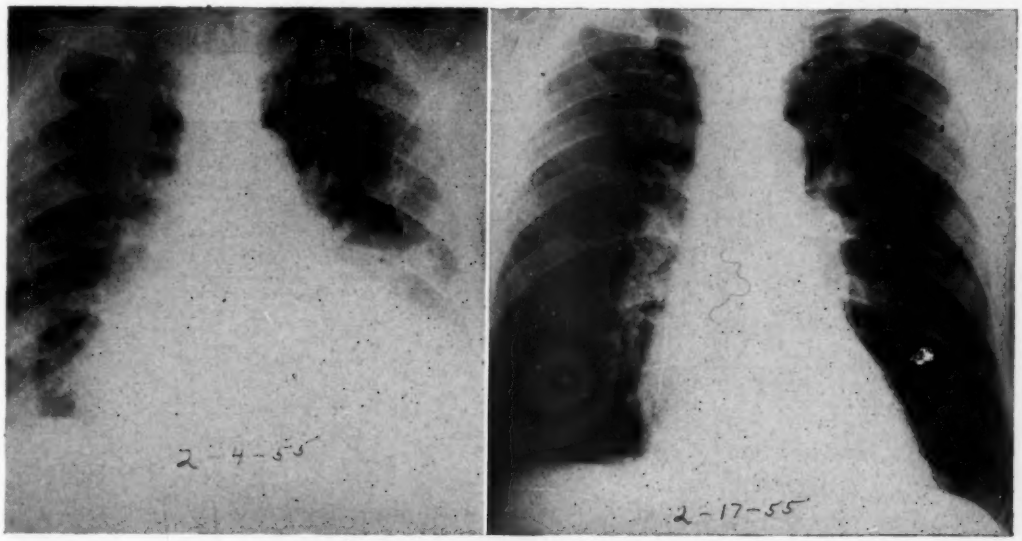
On February 9, thoracocentesis was done on the left side and 780 c.c. of intensely bloody fluid were aspirated. Aspiration was repeated 5 days later and again produced bloody exudate. No tumor cells nor acid-fast bacilli were found in the aspiration fluid. Culture of the exudate yielded no growth. Blood cultures remained sterile. Tests for L. E. cells were negative. From January 23 to February 6, the hemoglobin value dropped to 9.6 Gm.

Treatment with heparin and Dicumarol was started on the second day of illness (January 23). After two days heparin was withdrawn when the prothrombin time was 30 seconds. Administration of Dicumarol was discontinued after 6 days because of the drop in hemoglobin. The prothrombin time was consistently under 35 seconds, except on January 27, when it was 37 seconds. After withdrawal of Dicumarol the prothrombin time returned to normal. It ranged from 15 to 17 seconds on January 31, and on the following 2 days. The first sign of pleural involvement appeared 3 days after the prothrombin time had reached normal values.

In spite of the febrile complications the patient felt surprisingly well. Following the thoracocentesis rapid absorption of the pleural exudate took place. An x-ray study on February 17 (Fig. 2,*B*) showed decrease of pulmonary congestion and complete clearing of the pleural shadings in both lung fields. Comparison of the size of the heart with that of the previous study was rendered difficult by descent of the diaphragm. Nevertheless, decrease of the cardiac silhouette was obvious, particularly in the right portion of the middle shadow. After rapid clearing of the pleural fluid no trace of pulmonary infiltration could be discerned. This, in the opinion of the roentgenologist, weighed heavily against the diagnosis of pulmonary infarction. The patient was discharged on the twenty-eighth day of illness.

Summary: Myocardial infarction was accompanied by an unusually prolonged febrile period. A loud pericardial friction rub that was audible for 10 days, electrocardiographic changes, and enlargement of the cardiac shadow on x-ray supported a diagnosis of pericarditis with effusion. Signs of bilateral pleural effusion became manifest on the thirteenth day of illness. Thoracocentesis yielded

bloody fluid. There were none of the usual indications of pulmonary infarction. Anticoagulant therapy was used for 6 days only. The prothrombin time never exceeded therapeutic levels and had returned to normal 3 days before hemorrhagic pleural effusion became manifest.



A. *B.*

Fig. 2.—Case 2. *A*, Bilateral pleural effusion and enlargement of the heart silhouette. *B*, After 13 days the pleural effusions have subsided and the size of the heart silhouette has become normal.

3. *Hemorrhagic Pneumonia.*—

CASE 3.—M. M., a 52-year-old man, gave a history of rheumatic fever at the age of 28 years. His sister and niece also had rheumatic fever. The patient was hypertensive. In May 1952, he had suffered an anteroseptal wall infarction. On Feb. 13, 1956, he was seized with severe pressing pain in the mid-chest with radiation into both arms. He was admitted to the Maimonides Hospital on Feb. 14, 1956.

On admission the rectal temperature was 99.8° F. The blood pressure was 130/80 mm. Hg. The heart rate was 70 per minute. There was no evidence of congestive heart failure. The lungs were clear. A soft systolic murmur was audible in the apical area. The liver was not palpable. The abdomen was somewhat distended.

Laboratory findings: Urine was negative; hemoglobin 14 Gm. per 100 ml.; leukocyte count 18,000 per c. mm. with 77 per cent neutrophils and a shift to the left; sedimentation rate 16 mm. per hour; fasting blood sugar 129 mg. per cent; urea nitrogen 15 mg. per cent. An electrocardiogram taken on February 14, showed signs of a recent posterior wall infarction.

Course: On February 15, the third day of illness, the temperature rose to 102.2° F., and the patient appeared severely ill. He complained of a new kind of pain in the lower half of the sternum which was aggravated by breathing. A pericardial friction rub was heard. Respiration was rapid and shallow. A nonproductive cough was present. Homans' sign was negative. The calves were not tender to pressure. Examination of the lungs revealed signs of extensive consolidation. Over the right lower lobe there was marked dullness and loud bronchial breathing. Cracking râles were audible over both pulmonary bases. A portable x-ray study (Fig. 3,*A*) showed diffuse shadowing of the right hemithorax and pulmonary congestion at the left side. The transverse diameter of the heart was markedly enlarged and the cardiac waist was widened. The patient was given 2,400,000 units of penicillin and 2 Gm. of streptomycin daily.

On February 16, the pericardial friction rub was no longer audible. The patient was cyanotic and markedly dyspneic. Physical signs pointed to spread of the pneumonic process to the left

lung. Blood-tinged sputum was expectorated. The liver was palpable below the right costal arch. A mercurial diuretic was given and Chloromycetin was added to the antibiotics.

Administration of Dicumarol was started on February 14. The prothrombin time rose to 30 seconds on the fourth day of anticoagulant therapy. However, as a matter of precaution, Dicumarol was withdrawn on that day. Determinations of prothrombin time were continued for another 6 days. The readings were 32 and 36 seconds, respectively, on the first 2 days after discontinuation and 14 seconds on the following 4 days.

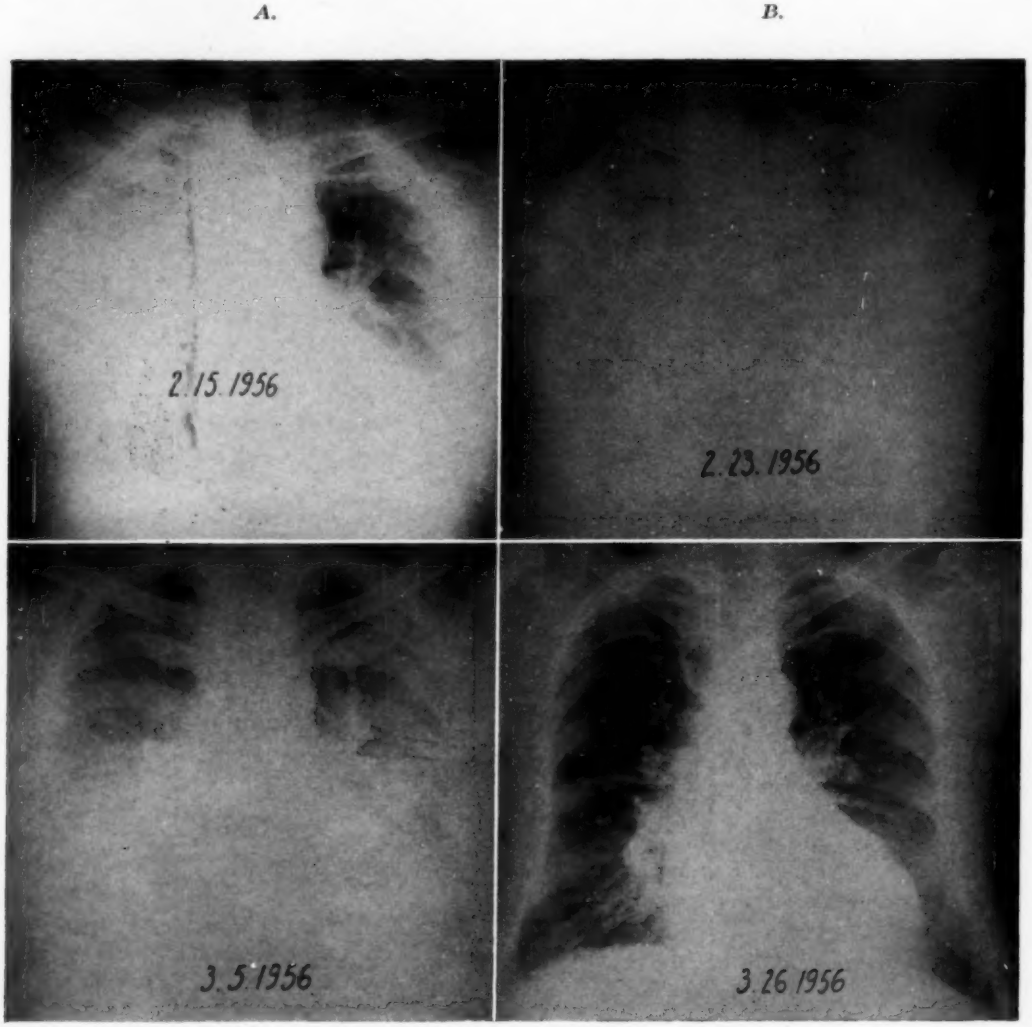


Fig. 3.—Case 3. *A*, **Feb. 15, 1956. Diffuse shadowing of the right hemithorax and pulmonary congestion at the left side.** *B*, **Feb. 23, 1956. Dense coalescent hazing of both lung fields.** *C*, **March 5, 1956. Clearing of both upper lung fields.** *D*, **March 26, 1956. Advanced clearing of both lungs.** *A*, *B*, **and** *C* **were bedside studies;** *D* **was a 6-foot film.**

The leukocyte count was 5,000 per c. mm. with 83 per cent neutrophils on February 23. The sputum became intensely hemorrhagic, but was never rusty. Repeated cultures and smears of the sputum revealed a variety of organisms including *Staphylococcus albus*, *Streptococcus nonhemolyticus*, Friedländer's bacillus and *Micrococcus catarrhalis*. No acid-fast bacilli were found in the sputum. Blood cultures remained sterile.

On February 18, the patient complained of pain in the right shoulder which was aggravated by breathing and cough. On February 21, pain shifted to the mid-chest region. The pulmonary process showed no signs of resolution. On the contrary, loud bronchial breathing became audible in the left axillary region. An x-ray study of the chest on February 23 (Fig. 3,*B*) showed dense coalescent hazing of both lung fields obscuring the cardiac and diaphragmatic outlines. The fever curve was of a plateau type, daily peaks of temperature ranging from 101° to 102° F. for a period of 1 week. Cyanosis and respiratory distress became more intense.

Since the pulmonary condition was apparently not influenced by the antibiotics, therapy with adrenal steroids was begun. Prednisone was given from February 21 to 28, starting with a daily dose of 35 mg., which was gradually reduced. The effect was gratifying. The temperature fell within 24 hours to 100.6° F., breathing became less labored, and cyanosis diminished. From then on clinical improvement was steady, if slow. Signs of resolution of the pulmonary process appeared. Bronchial breathing became less widespread and moist râles more numerous. An x-ray study on February 27, showed clearing of the left upper lobe. A pericardial friction rub was noted again on February 28. By March 4, the white blood count was 8,900. X-ray study on March 5 (Fig. 3,*C*) revealed clearing of both upper lung fields. The patient was allowed out of bed. On March 26, a 6-foot x-ray film (Fig. 3,*D*) showed advanced clearing of both lungs and moderate pulmonary congestion. The patient was discharged on the forty-fifth day of illness.

Summary: Acute myocardial infarction was complicated by pericarditis, pneumonitis, and pleurisy. Hemorrhagic pneumonia was the predominating complication. It developed on the third day of illness and spread rapidly, involving both lungs. No responsible microorganism was discovered. Antibiotics were of no avail. Improvement followed administration of cortisone. Dicumarol given initially was discontinued after 4 days. The prothrombin time was on 2 days only above 30 seconds, the maximum being 36 seconds. The pulmonary process lasted for about 4 weeks.

COMMENT

Since the introduction of anticoagulant therapy for myocardial infarction, there has been an understandable tendency to attribute hemorrhagic complications to this treatment. Nichol[1] and Goldstein and Wolff[2] reported on hemopericardium complicating acute myocardial infarction, which they felt was largely an effect of anticoagulant treatment. Goldstein and Wolff pointed out that the constantly moving granulating serous surfaces of the inflamed pericardium in the presence of anticlotting agents represent a potent source of hemorrhage. They stressed that hemorrhagic pericarditis should be suspected in the presence of (1) a prolonged and persistent or recurrent pericardial friction rub, (2) recurrence of cardiac pain, (3) vascular collapse accompanied by extended neck veins, and (4) demonstration of pericardial effusion. The authors advised against the continued use of anticoagulants in the presence of these signs.

Following the communication by Goldstein and Wolff other cases of hemopericardium complicating myocardial infarction were reported.[3-6] In some of these the diagnosis was supported by post-mortem study[4] or paracentesis[3,5,6]; in others[6] it was based on the diagnostic criteria mentioned by Goldstein and Wolff, while proof of the hemorrhagic character of the effusion was lacking. Anderson and co-workers[4] reported two instances of hemopericardium with recent myocardial infarction in which anticoagulant treatment was not used. Post-mortem study in one of the cases revealed that there was no rupture of the myocardium, epicardium, or coronary branch. The source of the hemorrhage was found to be

vascular granulation tissue in portions of the inflamed epicardium and pericardium remote from the site of the myocardial infarction. E. M. Goyette[7] observed two cases of myocardial infarction with hemorrhagic pericardial effusion in the absence of anticlotting effect. He felt that the complication "mimicked idiopathic pericarditis in every way." A case of acute myocardial infarction with hemorrhagic pericarditis was reported by Shipley[8] in the era prior to the clinical use of anticoagulant drugs. Our Patient 1 presents another example of bloody pericardial effusion for which anticoagulant treatment cannot be held responsible. Thus, pericarditis complicating myocardial infarction may be of hemorrhagic character in the presence of a normal clotting mechanism; and the criteria offered by Goldstein and Wolff are diagnostic of generalized pericarditis but do not necessarily indicate a hemorrhagic type of effusion.

The observation of hemorrhagic pericarditis in the presence of a normal clotting mechanism raises the question whether other hemorrhagic complications of myocardial infarction may not occur independently of anticoagulant therapy. Hemorrhagic pneumonia associated with acute myocardial infarction has been observed in post-mortem studies.[10] In our Cases 2 and 3 of hemorrhagic pleurisy and pneumonia, Dicumarol was used only for a few days; the prothrombin time did not exceed therapeutic levels and returned quickly to normal after anticoagulant therapy was discontinued. Hemorrhagic expectoration, however, (in Case 3) persisted for many days after return of the normal clotting mechanism. In Case 2 hemorrhagic pleurisy became manifest only after the prothrombin time had returned to normal. We have repeatedly observed hemorrhagic expectoration in the first few days of a recent myocardial infarction, when evidence of congestive heart failure, thrombophlebitis, or pulmonary emoblism was absent. We feel that in such instances, besides pulmonary infarction, left heart failure and anticoagulant effect, hemorrhagic pneumonitis should be considered as an etiological factor.

Recently, one of us (W. D.) described a complication of acute myocardial infarction[9] which was manifested by prolonged or recurrent attacks of fever and pleuropericardial pain; a pericardial friction rub persistent for many days or recurrent; pericardial and pleural effusions and pneumonitis. The complication was referred to as postmyocardial-infarction syndrome. It can be readily seen that the criteria of hemorrhagic pericarditis as stated by Goldstein and Wolff,[2] and attributed to the effect of anticlotting agents, are largely identical with the features of the postmyocardial-infarction syndrome. We believe that the instances of hemopericardium reported in the literature and our own cases fit the description of this syndrome and should be grouped under this heading. Among the significant features of the postmyocardial-infarction syndrome a tendency to hemorrhagic inflammation should be included.

The exact cause of the inflammatory conditions complicating myocardial infarction could not be elicited. Search for a responsible organism in blood, sputum, pleural, and pericardial effusions was unsuccessful. Antibiotics had no effect. Geever and associates[10] observed at autopsy in 3 cases of acute myocardial infarction "atypical pulmonary inflammatory reactions" which were apparently of nonbacterial origin. They remarked: "Their occurrence in individuals having

myocardial infarction must be more than coincidental." Case 1 described by these authors presented extensive bilateral bronchopneumonia with abundant bloody sputum and generalized pericarditis. It greatly resembles our Case 3. The authors pointed out that the microscopic features were similar to those of atypical and rheumatic pneumonia. It may be of interest that our Patient 3 presented a personal and family history of rheumatic fever.

Rich and Gregory[11] produced pulmonary lesions identical with those of rheumatic pneumonitis in the experimental animal by injection of horse serum or egg albumen. Ellis and McKinlay[12] reported on pneumonia associated with pericarditis and pleurisy which were caused by hypersensitivity to Prontosil. Gregory and Rich[13] stressed the similarity of the pulmonary lesions produced by injection of horse serum and those due to sulfonamide hypersensitivity. Harkavy[14] described the occurrence of allergic pneumonitis and serositis in patients suffering from bronchial asthma. McKinlay[15] reported on allergic pericarditis and pleurisy which developed following the injection of tetanus antitoxin. We feel that the inflammatory complications of acute myocardial infarction, including those of a hemorrhagic nature, may be likewise allergic in nature, representing a hypersensitivity reaction to autoantigens which result from necrosis of the myocardium.

SUMMARY

Three cases of acute myocardial infarction are reported which were complicated by hemorrhagic pericarditis, pleurisy, and pneumonia, respectively. Anticoagulant therapy was not used in the instance of hemorrhagic pericarditis, and was employed for only a few days in the other cases, the prothrombin time never exceeding therapeutic levels.

The cases of this report, and similar instances reported in the literature under the heading of hemopericardium complicating myocardial infarction, present features such as were described recently as characteristic of a postmyocardial-infarction syndrome. The inflammations constituting this syndrome may be of hemorrhagic character.

It is suggested that the postmyocardial-infarction syndrome is due to sensitization.

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ELECTROCARDIOGRAPHIC PATTERNS SIMULATING CORONARY OCCLUSION IN PATIENTS WITH CHRONIC RHEUMATIC CARDIOVALVULAR DISEASE

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IT IS the purpose of this communication to describe and discuss certain electrocardiographic patterns in the right precordial leads which simulate myocardial infarction due to coronary occlusion, but which may occur in chronic rheumatic cardiovalvular disease.

Except for the true, isolated posterobasal wall infarction, which manifests itself predominantly by the appearance of tall R waves and prominent upright T deflections in the right-sided precordial leads, coronary occlusion with myocardial necrosis is indicated by the appearance of "abnormal" Q waves. These may assume different configurations, such as QS, QR, qRS, or other bizarre forms. However, small q waves can be present also in the absence of disease. For example, the initial or "septal" vector which is represented by a primary r wave in Leads V_1 and V_2 appears as a small q in Leads I, aV_L, V_5 and V_6. This results from early vector forces directed to the right and anteriorly as projected onto the horizontal and frontal planes. Small, or narrow, initial downward deflections can also be seen normally in Leads III or aV_F as a result of the course of this same "septal vector" to the right and somewhat superiorly, as projected to the frontal plane. Figs. 1*A* and 1*B* demonstrate schematically the orientation of a normal spatial QRS loop in the horizontal plane projection, utilizing the cube system of electrode placement.[1] The initial or "septal vector" forces (darkened areas) are directed to the right and anteriorly. This early vector is seen to fall into the positive field of derivation of V_1, thus producing a small r wave initially. It is, however, located in the negative field of V_6, resulting in a small, early q wave. Fig. 1*C* represents the frontal plane projection of another normal QRS loop. The septal vector, again demonstrated by the darkened area, inscribes small, normal q waves in Leads II, III and aV_F, because of its orientation superiorly and to the right in the negative portions of the electrical fields of these particular leads.

Because the distinction between pathologic and normal configuration is so important, criteria of normality for Q waves are frequently being revised.

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Such criteria were first limited to the standard leads,[2] later to the Wilson precordial leads,[3,4] and most recently to the augmented unipolar limb leads of Goldberger.[5] However, no matter how rigidly one follows any set of rules, tracings which fulfill every recognized standard of myocardial infarction appear from time to time in patients who have apparently not sustained a previous coronary occlusion. As pointed out by Myers,[6-9] patients with hypertrophy of either the left or right ventricle, bundle branch block, electrolyte disturbances, cardiac dilatation, and arrhythmias, may present QRS complexes which can be mistaken for myocardial infarction. It is, therefore, important not only to be thoroughly familiar with the commonly accepted criteria for abnormality of Q patterns (vide infra), but to be cognizant of those conditions which, in the absence of infarction, may produce complexes fulfilling these criteria.

MATERIAL

The records of 220 consecutive cases of chronic rheumatic cardiovalvular disease, observed in the private practice of the senior author (A.M.M.), were analyzed. The diagnosis was confirmed in each case by history, clinical, roentgen, and electrocardiographic studies, as well as a continuous follow-up. Most of the patients have been seen periodically for years at monthly or biannual visits. In the remaining instances, the referring physician, the patient, or the family has been contacted yearly by means of a routine check system that has been utilized for more than a decade.

The group of 220 patient was divided into 107 men and 113 women, ranging in age from 6 to 72 years, with an average age of 42.2 years. In addition, electrocardiograms of 220 patients, examined during the same period of time, with no known heart disease and without abnormal clinical findings, were also studied. In this group, there were 164 men and 56 women, with an age range from 15 to 73 years and a mean of 45.8 years.

METHODS

The records of the 220 patients with rheumatic valvular disease were divided into four main electrocardiographic groups: those with abnormal patterns of distinct right ventricular hypertrophy, left ventricular hypertrophy, combined left and right ventricular hypertrophy, and those with an entirely normal 12-lead electrocardiogram. The criteria of Sokolow and Lyon[10] were used to determine the presence of left ventricular hypertrophy.* The criteria for right ventricular hypertrophy, also listed by Sokolow and Lyon,[11] were used.† Both these sets of values, as detailed in the footnote, are based on the amplitude of the R and depth of the S waves in the standard, unipolar extremity and the precordial leads. The onset of the "intrinsicoid deflection" or "ventricular activation time," as well as the RS-T segment and T-wave changes are also evaluated. The presence of combined ventricular hypertrophy was determined by referring to the criteria of Rosenman and Katz[12] for patients with rheumatic heart disease.‡

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*$R_1 + S_3 \geqq 25$ mm.; R V_5 or R $V_6 \geqq 26$ mm.; R $aV_L \geqq 11$ mm.; R $V_5 + S\ V_1 \geqq 35$ mm.; V_6 activation time $\geqq 0.06$ sec.; S-T segment depression $\geqq 5$ mm. in V_4, V_5 or V_6 or aV_L or aV_F.

†R $V_1 \geqq 7$ mm.; S $V_1 \leqq 2$ mm.; S $V_6 > 7$ mm.; R $V_1 + S\ V_5 \geqq 10.5$ mm. (above the age of 5 years); R $V_5 \leqq 4$ mm.; R/S $V_5 \leqq 1$; R $aV_R = 5$ mm.; $\frac{R/S\ V_5}{R/S\ V_1} \leqq .04$; R/S $V_1 > 4$ (under the age of 5 years); R/S $V_1 > 1$ (above the age of 5 years); ventricular activation time $V_1 \geqq .04$ sec.; T V_1 inverted with R $V_1 \geqq 5$ mm.

‡ECG evidence of left ventricular hypertrophy, as enumerated in the criteria of Sokolow and Lyon; indirect ECG evidence of right ventricular hypertrophy—clockwise rotation; electrical position other than horizontal or semihorizontal; P mitrale and/or auricular fibrillation.

The various criteria described above were applied to our "normal" control series of patients, none of whom was found to present evidence of heart disease. In planning the selection of electrocardiograms, any tracings with evidence of distinct left ventricular hypertrophy, right ventricular hypertrophy, or combined ventricular hypertrophy, as has been defined, were to be eliminated from this group. It has previously been reported[12] that the standards of Sokolow and Lyon for right and left ventricular hypertrophy are so modest as to result in many "false positives" among normal persons. Despite this observation, and in order to adhere as closely as possible to absolute normality, it was planned that any record among our normal group which fulfilled any of the criteria would be eliminated from consideration. In actual fact, the problem did not present itself, since none of our control group revealed evidence of abnormality by any criteria. Because moderate degrees of left or right axis deviation* may be seen in the standard leads of records of healthy persons, axis deviation was not considered reason for elimination of the electrocardiogram from the normal control group.

Since we were primarily concerned with the presence of "abnormal" Q deflections in the right precordial leads in both the normal and rheumatic heart groups, any records with additional abnormal Q waves in other leads, compatible with infarction, were to be eliminated. The significance of Q waves in the standard leads was evaluated by the criteria of Pardee,[2] which state that the normal Q wave must not exceed 25 per cent of the amplitude of the succeeding R wave nor be of a width greater than 0.04 second.

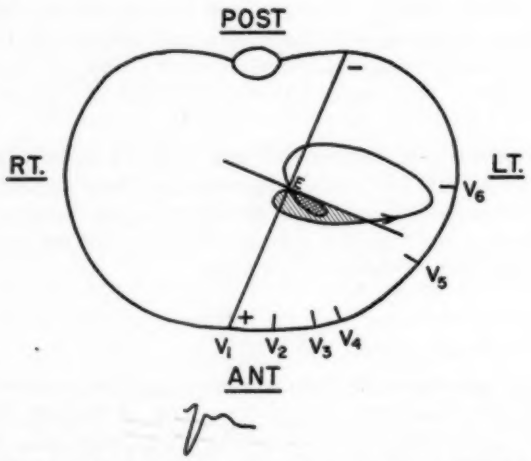

Fig. 1*A*.—Horizontal plane projection of a normally oriented spatial QRS loop. The arrow indicates the counterclockwise direction of inscription. The lead line of V_1 is seen to pass through the point of origin of vector forces, marked *E*. A perpendicular is drawn through *E*, separating the electrical field in relation to V_1 into a proximal or positive area and a distal or negative region. The darkened area represents the initial vector forces which fall into the positive field of V_1 and are represented by a small upright r wave in this lead.

RESULTS

None of the 220 patients, without known heart disease or evidence of specific chamber enlargement, displayed abnormal Q waves. Ordinary left axis deviation was present in 60 men and 17 women, among whom the average age was 48.2 years. Simple right axis deviation was seen in only 3 women and 1 man, whose average age was 30.5.

As indicated in Table I, in the group of 220 patients with documented evidence of chronic rheumatic cardiovalvular disease, there was predominant left

*Left axis deviation is present when the net value of the QRS complex in standard Lead I is a plus value and a minus value in Lead III and when the R wave is taller in Lead I than in Lead II. Right axis deviation is said to exist if the QRS complex in Lead III is more upright and positive than Lead II and when the net value of Lead I is minus.

ventricular hypertrophy present in 70 cases, 50 men and 20 women; predominant right ventricular hypertrophy in 11, 1 man and 10 women, while 3 men and 13 women fulfilled the criteria for biventricular hypertrophy. Twenty-five patients were without any evidence of chamber enlargement.

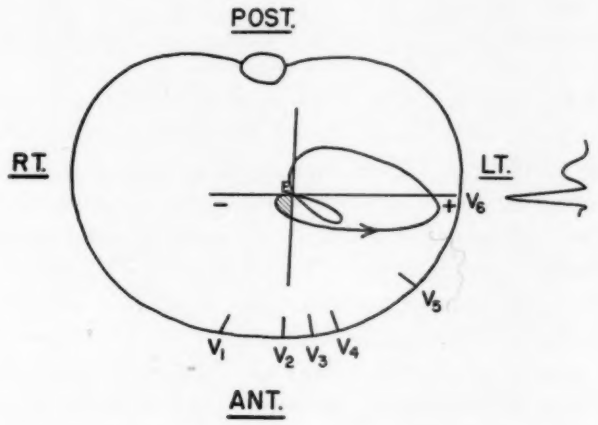

Fig. 1*B*.—The same normal horizontal plane projection of the QRS loop as in Fig. 1*A*. The lead axis of V_6 is schematically represented. The initial vector forces directed anteriorly and to the right pass into the negative field of V_6, resulting in an initial downward deflection of Q wave in V_6.

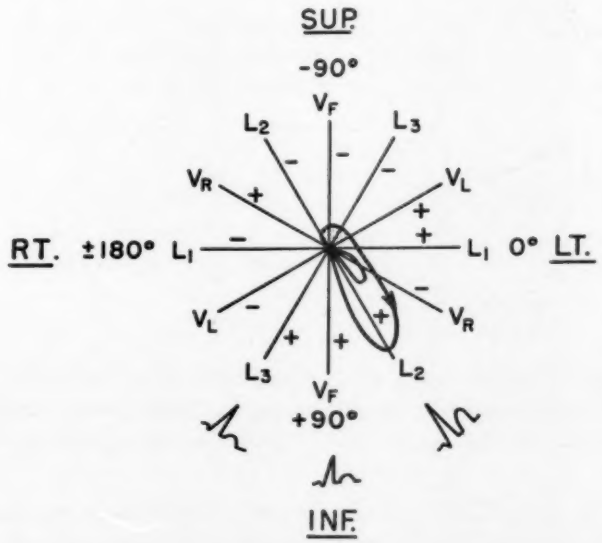

Fig. 1*C*.—This is the frontal plane projection of a normal spatial QRS vector. The arrow indicates a clockwise direction of inscription of the loop. The initial forces (darkened) are oriented superiorly and somewhat to the right. These early forces thus fall into the negative fields of Leads I, III, and aV_F, producing a small initial downward deflection or q wave in these leads. A hexaxial reference figure is employed here to portray the lead axes of derivation.

TABLE I. INCIDENCE AND SEX DISTRIBUTION OF AXIS DEVIATION IN 220 CASES OF CHRONIC RHEUMATIC CARDIOVALVULAR DISEASE

SEX	TOTAL NO.	LAD	RAD	LVH	RVH	BIVENT. HYPERT.
Male	107	51	4	50	1	3
Female	113	22	21	20	10	13

There was a total number of 15 records with abnormal Q waves (Table II), of which 9 were associated with electrocardiographic evidence of predominant left ventricular hypertrophy. Two others were the records of patients who had clinical and x-ray evidence of right ventricular hypertrophy, but who possessed strict electrocardiographic patterns of right bundle branch block, using the criteria of Wilson,[14] and Barker and Valencia.[15] The remaining 4 of the 15 cases with abnormal Q waves had definitely sustained previous coronary occlusion with myocardial infarction. Therefore, the 15 records which were abnormal from the Q-wave standpoint had the following distribution, as seen in Table II: 9 with left ventricular hypertrophy and no known coronary occlusion, 2 with right bundle branch block and no known myocardial infarction, and 4 with definite history of coronary occlusion with infarction. Thus, of 220 consecutive cases of chronic rheumatic cardiovalvular disease, there was a 5 per cent (11/220) incidence of "infarction-like" Q waves in V_1 and V_2. Among the 70 cases of predominant left ventricular hypertrophy the incidence of this phenomenon was 12.9 per cent (9/70). In patients with right-sided hypertrophy this abnormal pattern occurred in 18.1 per cent (2/11).*

TABLE II. AGE AND SEX DISTRIBUTION AND ECG DIAGNOSIS ASSOCIATED WITH 15 INSTANCES OF ABNORMAL Q WAVES

ECG DIAG.	LVH	RBBB	COR. OCCLUSION	TOTAL
Number	9	2	4	15
Average Age (yr.)	53	42	49.7	—
Sex	7 males 2 females	2 females	4 males	—

On the basis of auscultatory and other clinical criteria, in 3 cases of the 11 with no coronary occlusion Q waves appear to have involvement of the aortic valve alone, 2 of the mitral valve alone, and 4 both aortic and mitral valvular disease.

Both patients with right bundle branch block were women, aged 39 and 45 years, respectively, and had predominant mitral stenosis and a lesser degree of mitral insufficiency. In these cases, the bundle branch block probably reflects the presence of right ventricular hypertrophy.

*Per cents are given only as a guide and are not intended to imply statistical significance.

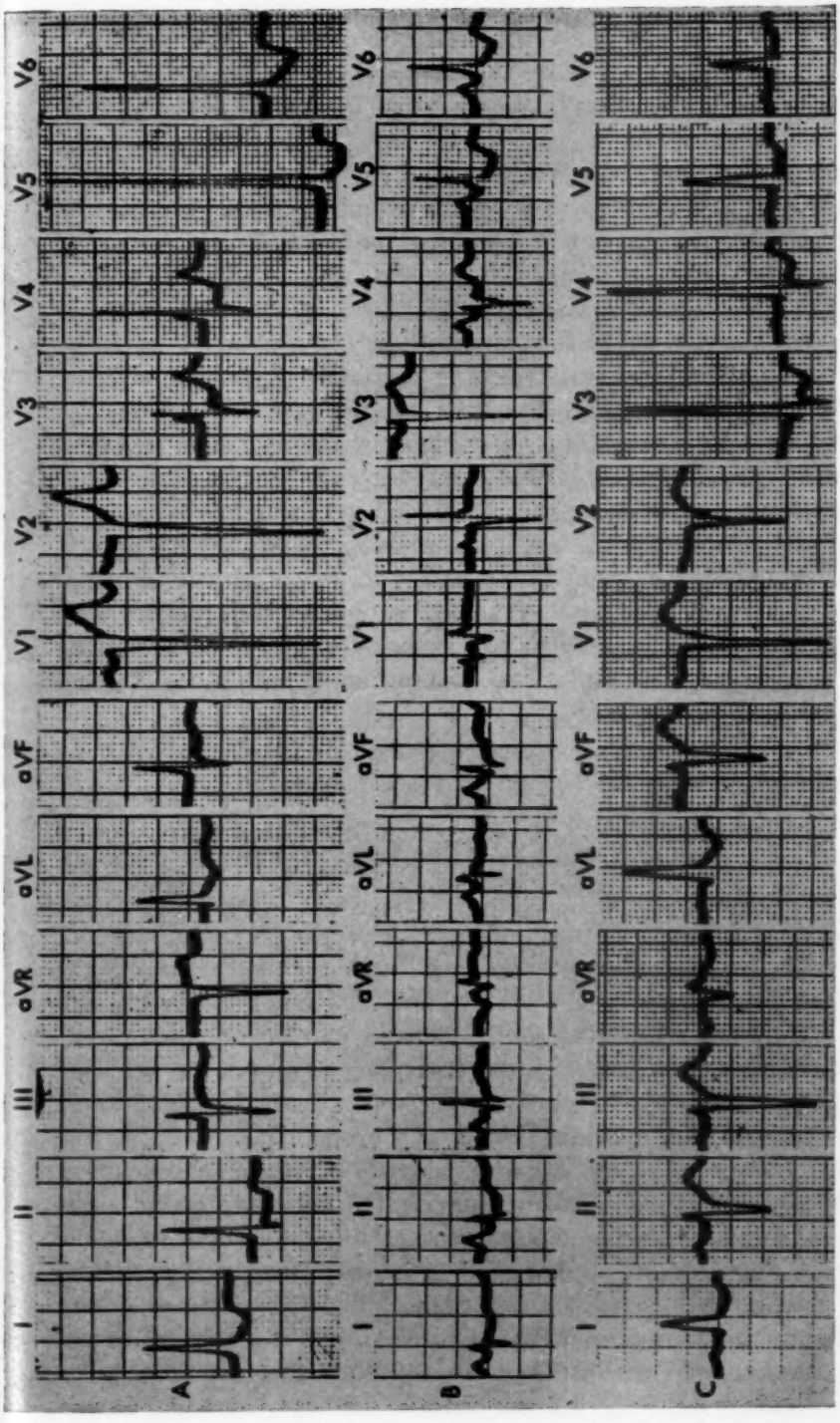

Fig. 2.—*A*, H. F., 45-year-old white man, with predominant aortic insufficiency, characterized clinically by typical auscultatory findings, "cor bovinum" roentgenographically, and wide pulse pressure (arterial pressure 154/66). Atrial fibrillation is present with an average ventricular rate of 84 per minute. Left axis deviation; markedly high voltage; deep, wide QS complexes in V_1 and V_2 and RS-T segment depression and diphasic or inverted T waves are found in Leads I, II, aV_L, and V_{3-6}. *B*, G. W., a 39-year-old white woman who clinically demonstrated evidence of predominant mitral stenosis, consisting of the classic auscultatory phenomena and x-ray configuration of a large left atrium and right ventricle with no apparent left ventricular hypertrophy. Regular sinus rhythm is present; right axis deviation; tall, prominent, peaked P waves, especially in Leads II and aV_F; delayed R in aV_R; QR in V_1; widened QRS (rSR′ in V_2); RS-T segment depressions and diphasic T waves in I, II, aV_F, and V_{4-6}. *C*, D. B., a 47-year-old man, with a clinical picture of acute coronary occlusion with myocardial infarction, preceded by a long history of angina. Physical examination disclosed the murmur of aortic stenosis. Roentgenologic studies showed moderate left ventricular hypertrophy. Regular sinus rhythm; left axis deviation; high voltage; deep, wide Q waves in V_1 and V_2, indistinguishable from those in *A*; RS-T segment depressions and diphasic T waves in Leads I, aV_L, and V_{3-6}.

Representative electrocardiograms from each of these three groups are reproduced. Fig. 2,*A* is the tracing of a 45-year-old white man with left ventricular hypertrophy or enlargement and no history of coronary occlusion. There is atrial fibrillation at an average ventricular rate of 84 per minute. The patient had never received digitalis. Note the deep QS complexes in Leads V_1 and V_2. The dominant valvular lesion in this case was aortic insufficiency with cor bovinum. The arterial pressure was 154/66 mm. Hg. Precordial pain was denied.

Fig. 2,*B* is the tracing of a 39-year-old white woman whose electrocardiogram fulfills the criteria of right bundle branch block. The P waves are prominent, wide and notched. Lead V_1 shows a deep, wide Q wave followed by a tall, delayed R. An rSR′ complex is seen in V_2. Lead aV_R also presents a late R wave. The QRS measures 0.11 second and there is a prolonged "intrinsicoid" deflection. The patient was not receiving digitalis. The predominant lesion in this case was mitral stenosis. Roentgen studies revealed a large left atrium, as evidenced by a double contour in the posteroanterior view and posterior displacement of the esophagus in the right anterior oblique projection. Right ventricular hypertrophy was also demonstrated by the x-ray films.

Fig. 2,*C* is a random electrocardiogram taken from a patient with rheumatic cardiovalvular disease who had sustained a coronary occlusion with myocardial infarction. Serial tracings in this case revealed progressive deepening and widening of the Q waves, associated with RS-T and T-wave changes, during a one-month period of hospitalization. The "infarction Q waves" in V_1 and V_2 are indistinguishable from those in Fig. 2,*A*.

DISCUSSION

The occurrence of abnormal QS or QR patterns in the right-sided precordial leads in cases of right and left ventricular hypertrophy has also been noted before. These studies include ample autopsy correlation.[6,7] Kossmann[16] presented statistical evidence that a QS may normally exist in V_1 in the absence of myocardial pathology. Goldberger[17] explained this configuration on the basis of rotational or positional factors. While post-mortem findings are not included in our study, there is nothing in the clinical picture and laboratory findings to indicate that coronary occlusion did take place in any of the 11 cases. Myers[6] reported 12 patients with left ventricular hypertrophy in which there were electrocardiograms similar to those of our own group represented in Fig. 2,*A*. None of his patients presented clinical or other evidence of infarction. At post-mortem, there was no demonstrable myocardial necrosis in any of the 12; 10 were found to have hypertrophied left ventricles and 2 hearts were devoid of pathology. These observations support the contention that this particular pattern of QS can exist in the absence of infarction.

Comparing the tracing of left ventricular hypertrophy without infarction (Fig. 2,*A*) with that associated with infarction (Fig. 2,*C*), the two records are seen to be almost identical. Both fulfill the criteria for left ventricular hypertrophy described above and used in our laboratory. If one were confronted with two such single tracings, the question as to whether myocardial infarction had occurred could not definitely be determined electrocardiographically. Fur-

thermore, unless one were presented with a clear-cut picture of acute coronary occlusion, the differential diagnosis might be equally difficult, since angina may often be present in patients with rheumatic valvular disease affecting the aortic and mitral valves.

The average ages of the infarction and noninfarction group fall within the coronary artery disease range. Even the predilection for males (7:2) in the simple left ventricular hypertrophy group adheres to the statistical sex difference in the incidence of coronary artery disease. Other than by a reliable history and a careful study of serial tracings in which RS-T segments are first elevated and T waves progressively inverted, we know of no other way to differentiate between the two patterns.

Serial tracings on the patient whose random record appears in Fig. 2,*C* revealed the classical evidence of the evolution of an anteroseptal infarction. There was gradual deepening and widening of the Q waves from V_{1-3} with associated RS-T segment and T-wave aberrations, as the infarct evolved over a period of one month. Such well-delineated, acutely progressive changes did not occur in repeated electrocardiograms in the case of left ventricular hypertrophy (Fig. 2,*A*). This serves to stress the fact that caution must be observed in attempting to interpret any single tracing.

Though the electrocardiogram (Fig. 2,*B*), previously described, reveals a QR complex in V_1 which fulfills the criteria for infarction ($Q \geqq 25$ per cent of the succeeding R wave and $\geqq 0.04$ sec.), one is less likely to confuse it with an infarction pattern. Abnormal P waves, right axis deviation, a delayed R wave in aV_R and a widened QRS complex (rSR′) in V_2 are present. These findings are suggestive of right bundle branch block. Q waves in the right-sided precordial leads have been described in right ventricular hypertrophy without coronary occlusion.[7] It has been shown that the Q wave may in some instances be apparent and not real, a small initial r wave being buried in the isoelectric line of the preceding P-R interval.[18] Simultaneous right-sided precordial leads can establish the presence of a preceding isoelectric r before the apparent Q wave. Having disclosed a rSR′ pattern and not a QR complex in V_1 or V_2, by demonstrating an initial r wave in those leads, the significance of the rSR′ can then be conclusively determined by vectorcardiographic study as being right bundle branch block, right ventricular hypertrophy, or a normal variant.

This study reveals that the possibility exists of noncoronary occlusion Q waves appearing in V_1 and V_2, but not as far as V_3, in the absence of myocardial infarction, in patients with chronic rheumatic cardiovalvular disease.

CONCLUSIONS

Abnormal QS or QR patterns, occurring in V_1 and V_2, in the absence of myocardial infarction, may be seen in patients with chronic rheumatic cardiovalvular disease and consequent ventricular enlargement. This phenomenon was not present in 220 otherwise "normal" electrocardiograms. When left ventricular hypertrophy predominates, QS deflections in V_1 and V_2, identical to those seen in anteroseptal infarction, may appear. These may possibly be

distinguished from the true infarcts by serial studies. Random examination of any single tracing cannot be relied upon.

In lesions producing right ventricular hypertrophy, other features of the electrocardiogram may help to exclude infarction. When a QR pattern appears in V_1, as the result of right ventricular hypertrophy or an isoelectric r, the problem may be clarified by leads taken to the right of V_1, by simultaneous recording of precordial leads or by vectorcardiographic study.

Since angina may appear in the presence of aortic and mitral valvular disease, precordial pain may not be a reliable guide in the differential diagnosis of the abnormal Q deflections.

QS or QR patterns in V_1 and V_2 are not conclusive evidence of infarction, particularly when other signs of ventricular hypertrophy are present.

SUMMARY

1. Two hundred and twenty consecutive cases of chronic rheumatic cardiovalvular disease and 220 "normal" records are reviewed and compared.

2. None of the normals showed abnormal Q-wave patterns in V_1 and V_2.

3. Of the group with known chronic rheumatic cardiovalvular disease, 15 showed tracings compatible with interpretation of myocardial infarction due to coronary occlusion.

4. Only 4 of the 15 had other definite evidence of infarction. The remaining 11 cases with infarction-like QS patterns in V_1 and V_2 are not believed ever to have sustained coronary occlusions. Thus, a QS pattern in V_1 and V_2, not as far as V_3, may be observed in chronic rheumatic heart disease in the absence of coronary occlusion.

5. Representative tracings from patients with right ventricular hypertrophy and left ventricular hypertrophy, without clinical suggestion of infarction, are compared with the electrocardiogram of a case of anteroseptal infarction.

6. Techniques are mentioned by means of which a QS or QR pattern in V_1 and V_2, seen in instances of right ventricular hypertrophy or right bundle branch block, may be clarified.

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CONGENITAL DEAF-MUTISM, FUNCTIONAL HEART DISEASE WITH PROLONGATION OF THE Q-T INTERVAL, AND SUDDEN DEATH

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A COMBINATION of deaf-mutism and a peculiar heart disease has been observed in 4 children in a family of 6. The parents were not related, and were, as the other 2 children, quite healthy and had normal hearing.

The deaf-mute children, who otherwise seemed quite healthy, suffered from "fainting attacks" occurring from the age of 3 to 5 years. By clinical and roentgen examination, which was performed in 3 of the children, no signs of heart disease could be discovered. The electrocardiograms, however, revealed a pronounced prolongation of the Q-T interval in all cases.

Three of the deaf-mute children died suddenly at the ages of 4, 5, and 9 years, respectively.

CASE REPORTS

Case 1. Tormod J., born 1944.—This boy had suffered from repeated "fainting attacks" since the age of 3 years. The attacks occurred at intervals of up to 6 months, and they never lasted for more than 2 to 3 minutes. The attacks usually occurred following efforts. His relatives stated that the attacks were associated partly with pallor and partly with cyanosis, but never with convulsions or biting of the tongue. Involuntary emptying of the bladder, however, had been observed. Occasionally the boy had complained of palpitations and precordial pains.

In July, 1953, he was examined at Aust-Agder and Arendal Central Hospital (Dr. Kloster). The only pathologic finding was a prolongation of the Q-T interval in the electrocardiogram. On the assumption that he might be suffering from epilepsy, the patient was treated with barbiturates and phenantoin, without effect, however.

Since 1952, the boy attended a boarding school for deaf-mute children. On Oct. 10, 1953, he suddenly fainted without apparent cause. He remained unconscious for about 5 minutes with cyanosis of the face and with convulsive movements of the fingers. Afterwards he was somewhat exhausted, but after a few hours in bed, he was just as lively as usual and wanted to go out playing.

The boy was admitted to the Medical Department of Vestfold Central Hospital where he was observed from Oct. 13, to Nov. 10, 1953. Apart from the deaf-mutism, no evidence of congenital defects could be discovered. He had a healthy appearance. Height: 142.5 cm.; weight 34.6 kilograms. His deaf-mutism to some extent prevented adequate contact, but he appeared normally developed and was cooperative when examined.

The physical examination revealed no essential abnormality. The pulse was 72, with regular rhythm, blood pressure 100/60 mm. Hg. The temperature was normal and there was no cyanosis or congestion. A weak systolic murmur (Grade 1) was heard in the second left intercostal space. Neurological examination revealed nothing abnormal.

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Laboratory findings were: basal metabolic rate +7; serum calcium: 10.5 mg. per 100 ml.; serum phosphorus: 4.1 mg. per 100 ml.; serum potassium: 4.8 meq. per liter. Glucose tolerance test gave a normal response without evidence of hypoglycemia. Erythrocyte sedimentation rate: 8 mm. per hour; hemoglobin: 81 per cent. The urine was normal and Meinicke's reaction was negative.

X-ray examination showed a heart shadow of normal size and shape. The electrocardiogram, which will be discussed later, showed a pronounced prolongation of the Q-T interval (Figs. 1 through 5).

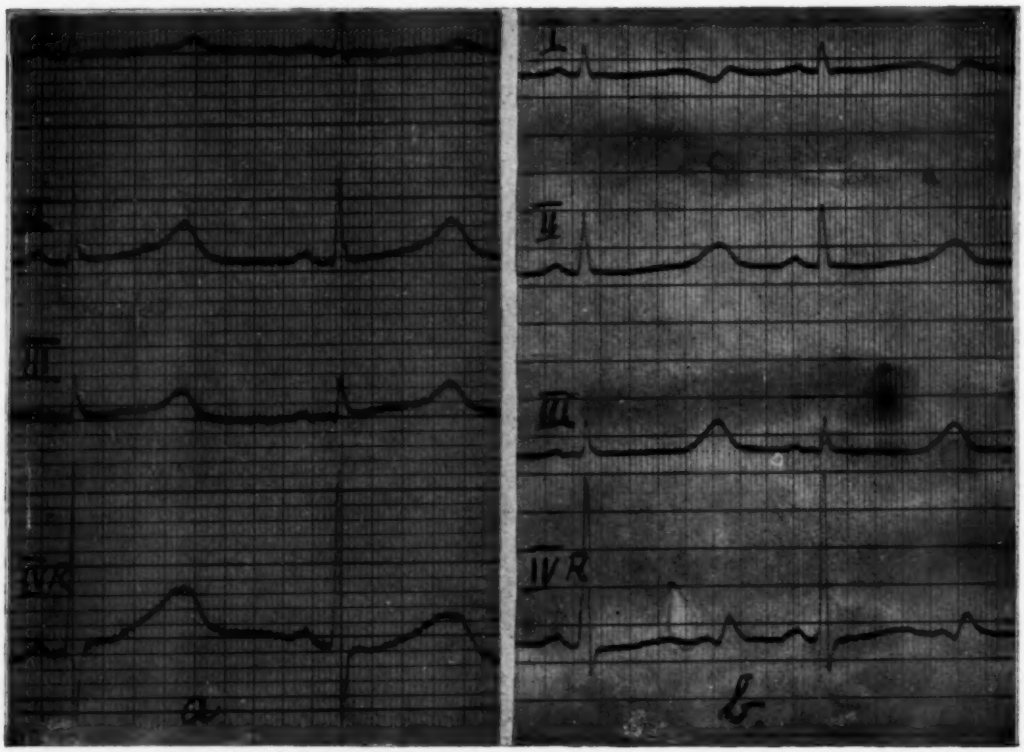

Fig. 1.—Tormod J. (*a*) ECG July 20, 1953, during rest. Leads I, II, III, IV R. Q-T = 0.50 sec. R-R = 0.88 sec. (*b*) ECG July 20, 1953, after stair-running. Leads I, II, III, IV R. Q-T = 0.60 sec. R-R = 0.86 sec.

On Nov. 19, 1953, one week after his discharge, he had another attack. He suddenly became pale and fell unconscious. On the doctor's arrival the patient was pulseless with cold skin and with marked cyanosis. He was taken to the hospital as soon as possible, but on arrival he presented definite signs of death with marked hypostasis. There was no frothy discharge from the nose or mouth.

Autopsy.—At autopsy on the following day, distinct livores were seen in the face and dependent areas. The lungs showed moderate hypostasis and subpleural hemorrhages. The heart weighed 195 grams and was well contracted. The coronary orifices were normal, as were the 3 major branches of the coronary arteries. There was no hypertrophy or visible lesion of the myocardium. Some small atheromatous streaks were seen in the intima of the aorta just distal to the aortic valves. There was no patency of ductus arteriosus or foramen ovale. The endocardium had a normal appearance, with normal orifices and heart valves.

The thymus gland was not definitely enlarged, weighing 43 grams. The abdominal organs including the adrenals (total weight 12 grams) and spleen (120 grams) were normal.

Microscopic Examination.—Examination by Professor L. Kreyberg of the heart muscle (left and right ventricles, interventricular septum) was reported as follows: "Microscopical exami-

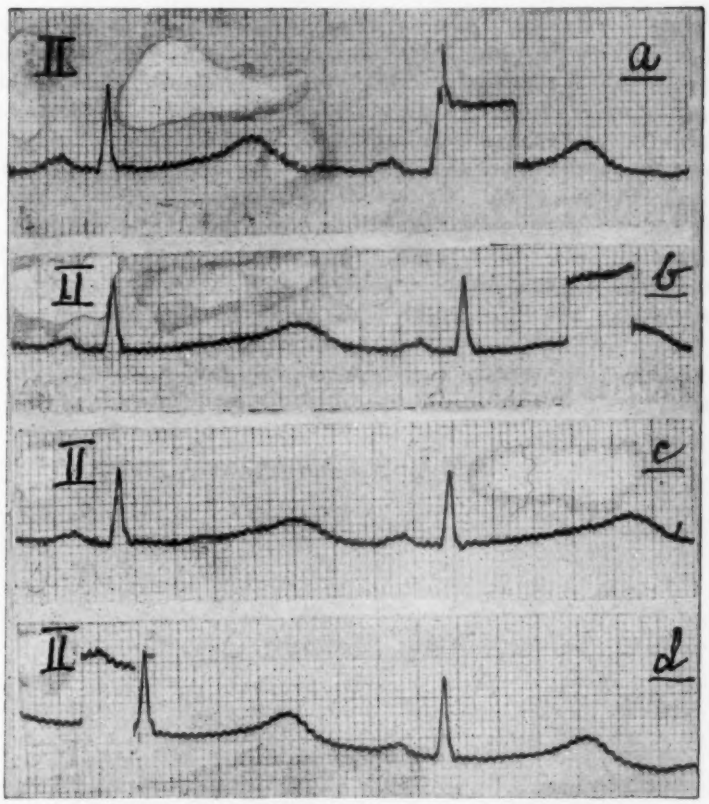

Fig. 2.—Tormod J. ECG Oct. 22, 1953. Lead II: (*a*) Prior to adrenalin. Q-T = 0.50 sec. R-R = 0.84 sec.; (*b*) 20 minutes after 0.10 mg. Adrenalin subcutaneously. Q-T = 0.62 sec. R-R = 0.88 sec.; (*c*) 30 minutes after Adrenalin. Q-T = 0.60 sec. R-R = 0.84 sec. (*d*) 60 minutes after Adrenalin. Q-T = 0.50 sec. R-R = 0.74 sec.

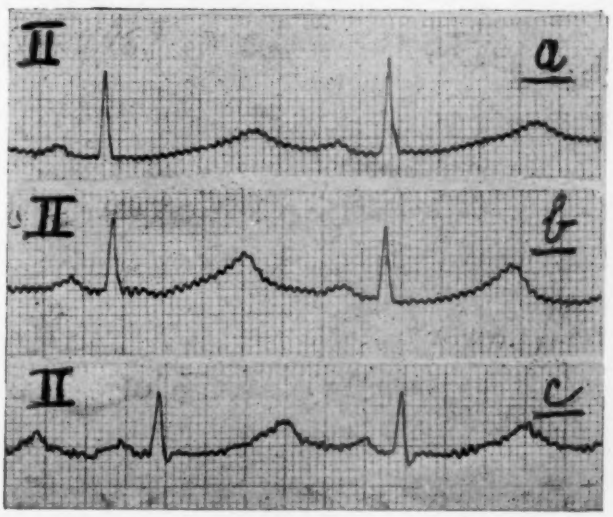

Fig. 3.—Tormod J. ECG Oct. 26, 1953. Lead II: (*a*) Prior to atropine. Q-T = 0.48 sec. R-R = 0.74 sec. (*b*) 20 minutes after 0.50 mg. atropine sulfate subcutaneously. Q-T = 0.44 sec. R-R = 0.68 sec. (*c*) 30 minutes after atropine. Q-T = 0.40 sec. R-R = 0.62 sec.

nation of the heart reveals closely adjacent muscle fibers of approximately the same diameter and with well preserved cross-striations. The nuclei are of oval shape and centrally located within the fibers. Around the nuclei, or more irregularly distributed in the fibres, there are small collections of minute granules giving positive Schiff reaction after treatment with periodic acid. There is no increase of the connective tissue, and no scars are seen.

The microscopic appearance of the other organs is essentially normal, apart from a slight hyperplasia of the thymus gland. *Conclusion:* Heart muscle, adrenals and spleen without pathological changes. Slight hyperplasia of the thymus gland."

Case 2. Hjördis J., born 1948.—This girl died suddenly in 1953, at the age of 5 years. Some months previously she had suffered two "fainting attacks," one occurring after swimming and the other after running. She died suddenly while picking berries. She had never had a medical examination.

Case 3. Ellen J., born 1950.—On two occasions in 1955, she had attacks of "slight fainting" without complete loss of consciousness. A clinical and x-ray examination of the heart on Aug. 12,

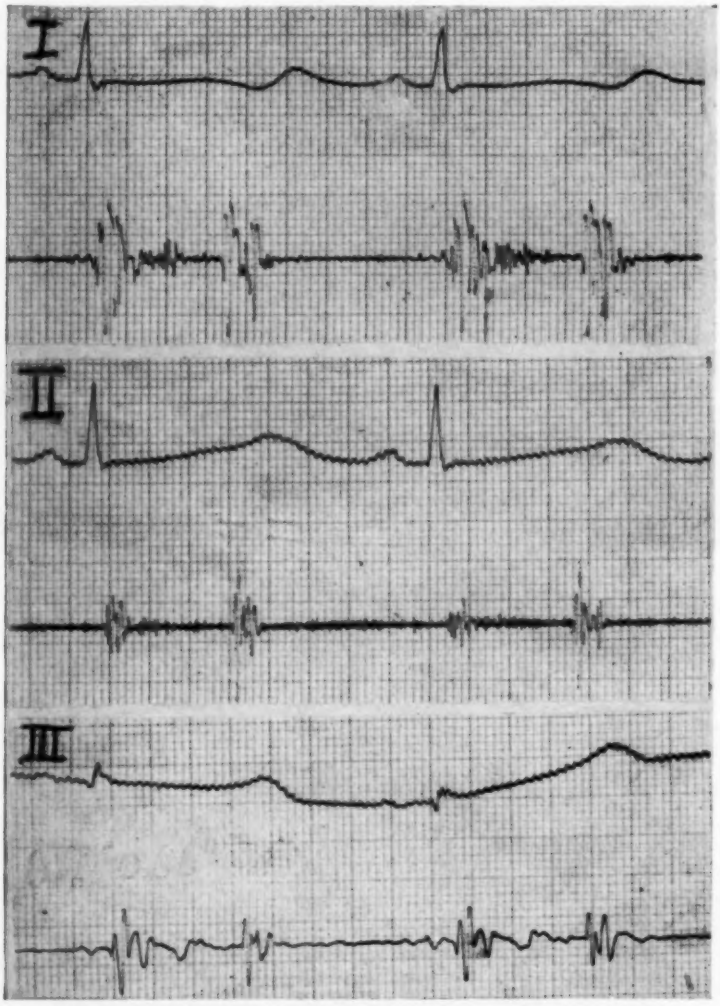

Fig. 4.—Tormod J. ECG (Leads I, II, III) and phonocardiogram Oct. 30, 1953, after quinidine medication (quinidine sulfate 0.20 Gm. × 3 the day before and 0.20 Gm. at 11 A.M. and at 3 P.M. on day of examination. Records made at 5 P.M.). Q-T = 0.60 sec. Interval from onset of first sound to onset of second sound = 0.32 sec. R-R = 0.86 sec.

1955, (Dr. Kloster) revealed no evidence of heart disease. The electrocardiogram showed prolongation of the Q-T interval (Fig. 6,*a*). Another electrocardiogram from Jan. 12, 1956, showed the same Q-T prolongation and also an inverted T in Leads I and IV R (Fig. 6,*b*).

Case 4. Anne-Marie J., born 1952.—In 1955, she suffered two "fainting attacks," one mild and the other severe. During the severe attack she was unconscious for 3 or 4 minutes, and appeared to be about to die. Convulsions were not observed during the attack. A clinical and x-ray examination of the heart on Aug. 12, 1955, (Dr. Kloster) showed nothing abnormal. In the electrocardiogram a marked prolongation of the Q-T interval was seen (Fig. 7,*a*). On Dec. 3, 1955, the ECG also showed flattening of the T waves.

On Feb. 9, 1956, while out playing with her sisters, she suddenly fell to the ground dead.

The parents and the two normal children born 1943 and 1946, respectively, had never had attacks of fainting. A clinical and x-ray examination of the heart on Dec. 3, 1955, (Dr. Kloster) gave no evidence of disease. The electrocardiograms were also normal, with the exception that the electrocardiogram of the child born in 1946, showed a prolonged P-Q interval (0.24 sec.) while the Q-T interval was quite normal.

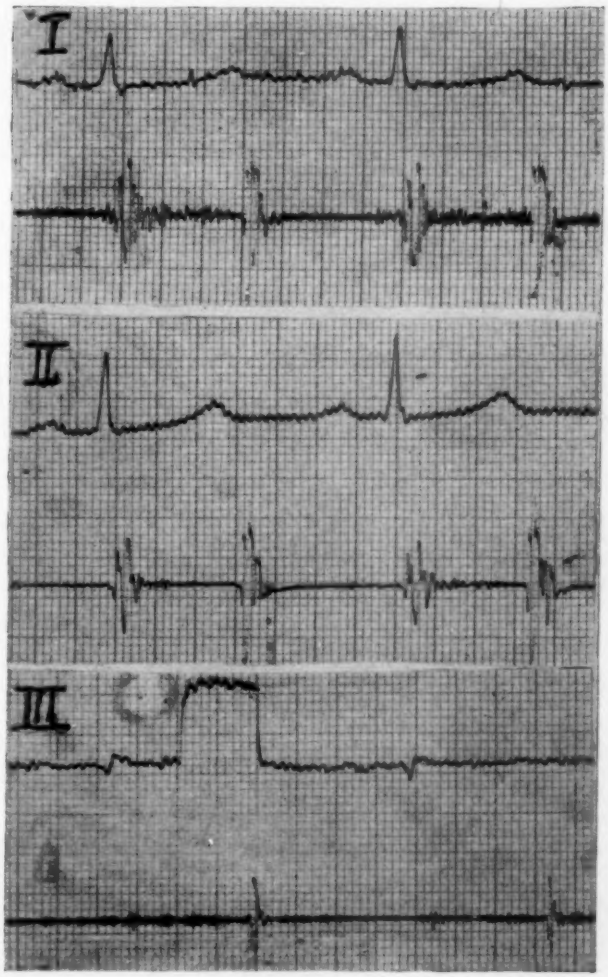

Fig. 5.—Tormod J. ECG (Leads I, II, III) and phonocardiogram Nov. 4, 1953, after digitalis medication (digitalis 1 I.U. × 3 on 3 previous days). Q-T = 0.36 sec. Interval from onset of first sound to onset of second sound = 0.32 sec. R-R = 0.72 sec.

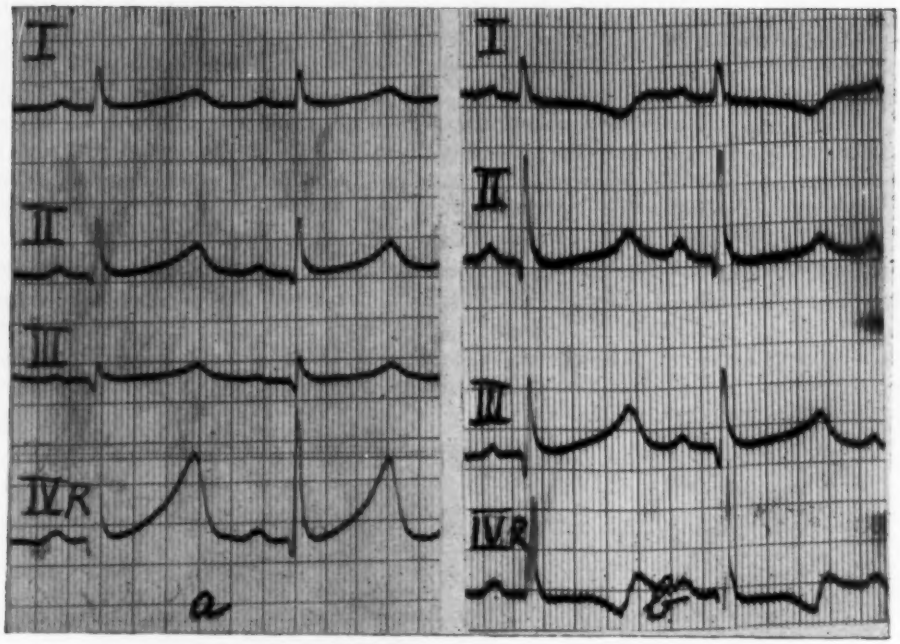

Fig. 6.—Ellen J. (*a*) ECG Aug. 12, 1955. Leads I, II, III, IV R. Q-T = 0.40 sec. R-R = 0.64 sec. (*b*) ECG Jan. 12, 1956. Leads I, II, III, IV R. Q-T = 0.42 sec. R-R = 0.62 sec. T I, T IV negative.

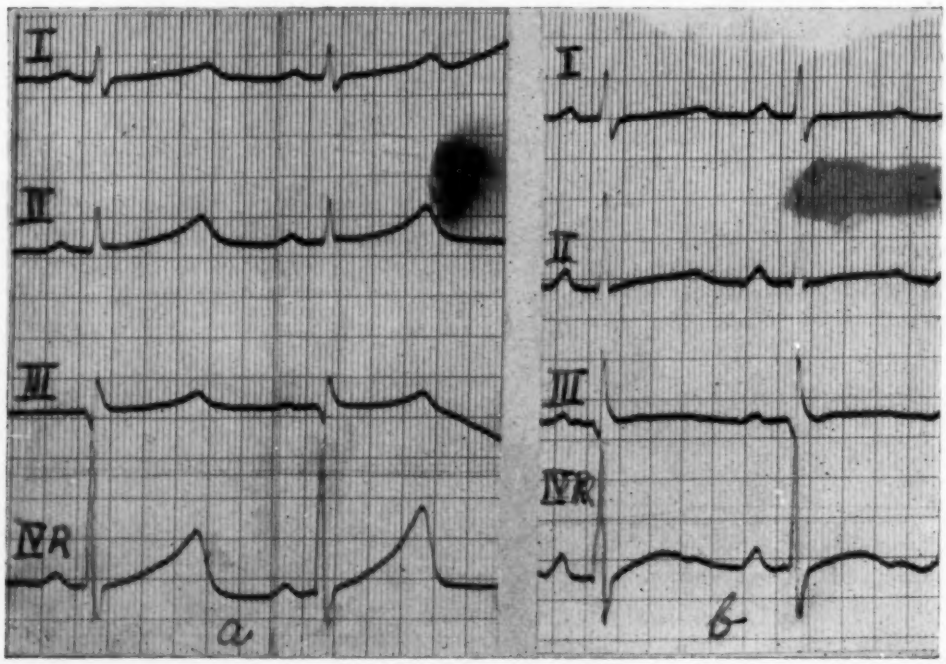

Fig. 7.—Anne-Marie J. (*a*) ECG Aug. 12, 1955. Leads I, II, III, IV R. Q-T = 0.42 sec. R-R = 0.72 sec. (*b*) ECG Dec. 3, 1955. Leads I, II, III, IV R. Q-T = 0.40 sec. R-R = 0.62 sec.

ELECTROCARDIOGRAPHIC FINDINGS

It can be discussed as to whether the end-deflection in these cases should be interpreted as T waves, U waves, or perhaps T-U waves.[4,10,11] Lepeschkin and Surawicz[4] suggest "consideration of every case in which the beginning of the second heart sound precedes the apparent end of the T-wave more than 0.07 second, as a possible case of merging of T and U." The electrocardiograms in our cases did not give any possibility to decide the question about T or U waves. The abnormal complexes in these cases were, in our opinion, caused by a delayed repolarization of the heart muscle. The question of nomenclature, therefore, seems to be of less importance. When making use of the term Q-T interval, however, we are well aware of the possible merging of T and U waves.

Numerous electrocardiographic recordings were made in Case 1, while the boy was under hospital care, viz., during rest, after exercise, and after administration of atropine, Adrenalin, digitalis, and quinidine. The results are presented in Figs. 1 to 5, and in Table I.

TABLE I

	R-R (SECOND)	Q-T (SECOND)	NORMAL UPPER LIMIT OF Q-T INTERVAL BY LJUNG'S FORMULA (SECOND)	Q-T PROLONGATION. PER CENT ABOVE UPPER LIMIT OF NORMAL	P-Q (SECOND)	MECHANICAL SYSTOLE (SECOND)
Tormod J., born 1944						
Fig. 1(*a*) July 20, 1953, during rest	0.88	0.50	0.40	25	0.14	
(*b*) July 20, 1953, after stair-running	0.86	0.60	0.39	54	0.12	
Fig. 2(*a*) Oct. 22, 1953, prior to Adrenalin	0.84	0.50	0.39	28	0.14	
(*b*) 20 minutes after 0.10 mg. Adrenalin subcutaneously	0.88	0.62	0.40	55	0.14	
(*c*) 30 minutes after Adrenalin	0.84	0.60	0.39	55	0.15	
(*d*) 60 minutes after Adrenalin	0.74	0.50	0.37	35	0.14	
Fig. 3(*a*) Oct. 26, 1953, prior to atropine	0.72	0.48	0.36	33	0.14	
(*b*) 20 minutes after 0.5 mg. atropine subcutaneously	0.68	0.44	0.36	22	0.14	
(*c*) 30 minutes after atropine	0.62	0.40	0.34	18	0.12	
Fig. 4. — Oct. 30, 1953, after quinidine	0.86	0.60	0.39	54	0.14	0.32
Fig. 5. — Nov. 4, 1953, after digitalis	0.72	0.36	0.36	0	0.16	0.32
Ellen J., born 1950						
Fig. 6(*a*) Aug. 12, 1955	0.64	0.42	0.35	20	0.14	
(*b*) Jan. 12, 1956	0.62	0.42	0.34	24	0.14	
Anne-Marie J., born 1952						
Fig. 7(*a*) Aug. 12, 1955	0.72	0.42	0.36	15	0.14	
(*b*) Dec. 3, 1955	0.62	0.40	0.34	18	0.14	

The predominant feature was a prolongation of the Q-T interval. Table I shows the values observed and the upper normal values as calculated by the formula of Ljung[8] ($Q-T = R-R \times 0.2 + 0.18 \pm 0.04$ sec.). In a case like this, with such marked deviations from the normal values, Ljung's formula

is sufficiently accurate. As shown by the figures and the table, the Q-T interval under normal conditions exceeded the upper normal limit by 25 to 33 per cent (Figs. 1,*a*, 2,*a*, and 3,*a*). Following exercise (Fig. 1,*b*) the prolongation increased to 54 per cent; after subcutaneous injection of 0.10 mg. Adrenalin (Fig. 2) to 55 per cent; and after quinidine (Fig. 4) to 54 per cent above the normal maximum. On the other hand, the Q-T interval decreased to 18 per cent above normal after 0.5 mg. of atropine subcutaneously (Fig. 3), and to a value corresponding to the normal upper limit after digitalis medication (Fig. 5).

Along with the prolongation of the Q-T interval following exercise, a negative T wave occurred in Lead I, and a diphasic T wave in Lead IV (Fig. 1,*b*). After quinidine medication diphasic T waves were observed in Lead I (Fig. 4).

The P-Q interval varied from 0.12 sec. after efforts and atropine to 0.16 sec. after digitalis medication. No correlation was found between the variation in P-Q and Q-T intervals.

The QRS complex showed no definite abnormality. Simultaneous registration of electrocardiogram and phonocardiogram were made following digitalis and quinidine medication (Figs. 4 and 5). Despite the highly different Q-T intervals, 0.36 sec. and 0.60 sec., respectively, the interval from the onset of the first sound to that of the second was the same in both instances. This demonstrated that the prolongation and variation of the electrical systole was not accompanied by changes of the mechanical systole which remained of normal and constant duration.

In Cases 3 and 4 the electrocardiograms also showed a prolongation of the Q-T interval (Figs. 6 and 7; Table I), but not so marked as in Case 1. The last electrocardiogram in Case 3 also had a negative T I and T IV.

DISCUSSION

The following questions arose: (1) What was the nature of the heart disease in these children? and (2) Was there any connection between the patients' cardiac disease and the deaf-mutism?

1. *Nature of the Heart Disease.*—The clinical picture was the same in all 4 cases. From the age of 3 to 5 years, they all suffered "fainting attacks," some mild, others severe. Three of the children died in such attacks. The nature of the attacks is uncertain, but most likely they can be explained as Adams-Stokes attacks caused by sudden standstill of the heart.

In Cases 1, 3, and 4 the electrocardiographic examination showed a marked prolongation of the Q-T interval; in Case 1 and 3 a negative T I and T IV were found occasionally. Apart from the electrocardiographic abnormalities no signs of heart disease could be demonstrated, either clinically or by x-ray examination. The post-mortem examination of the heart in Case I, the only case in which an autopsy was performed, revealed no evidence of heart disease.

The conformity of the clinical pictures and of the electrocardiographic abnormalities makes it evident that the 4 deaf-mute children were all suffering from the same kind of heart disease. The nature of this, however, is quite obscure.

A prolonged Q-T interval in the presence of a normal or shortened duration of the mechanical systole is a phenomenon which Hegglin[1,2] has termed "energetic-dynamic insufficiency of the heart." This is seen in certain disturbances in the myocardial metabolism caused by disturbed electrolyte balance, abnormal sugar metabolism, or hypothyroidism. In hypocalcemia, on the other hand, there is a prolongation of both the electrical and mechanical systole.[1-3,6-9] In our Case 1 clinical and laboratory examinations were made to reveal any of the above-mentioned causes. The patient, however, presented no signs of tetany or paroxysmal paralysis. The blood levels for calcium, phosphorus, and potassium were normal. There were no signs of hypothyroidism, and a glucose tolerance test gave a normal response.

None of the previously known causes of increased Q-T duration, therefore, explains the condition in our cases. Most probably we are dealing with a congenital anomaly of the myocardial metabolism with delay of the repolarization phase, caused by some enzymatic deficiency. In this connection it is of interest that quinidine prolonged the Q-T interval, while digitalis shortened it. This observation indicates an important effect of quinidine and digitalis on the repolarization of the heart muscle.

2. *Possible Connection Between the Heart Disease and the Deaf-Mutism.*—The coexistence of deaf-mutism and this peculiar heart disease in 4 children in one family hardly can be considered purely incidental. However, as neither the cause of the heart disease nor of the deaf-mutism is known, any attempt to explain the connection is purely speculative.

Lindenov[5] in his monograph on deaf-mutism reported several cases with coexistent defects. No case, however, of deaf-mutism with coexistent heart disease has been reported, and especially no case with prolonged Q-T interval.

SUMMARY

Four cases of deaf-mutism combined with a peculiar heart disease have been observed in one family. The parents and 2 other children were healthy and had normal hearing. The deaf-mute children all suffered attacks of fainting, probably Adams-Stokes seizures caused by standstill of the heart. The first attack occurred between the ages of 3 and 5 years, and 3 of the children died in such attacks at the ages of 4, 5, and 9 years, respectively.

Electrocardiographic studies in 3 of the cases revealed a marked prolongation of the Q-T interval. However, no clinical or roentgenologic evidence of organic heart disease was disclosed.

Autopsy was performed in one of the children. No gross abnormality of the heart was revealed, and the microscopic appearance of the heart muscle was normal. In this case a further prolongation of the Q-T interval followed exercise and quinidine medication, while a shortening was observed after atropine and particularly after digitalis medication. Following effort and quinidine medication, changes in the T waves were observed, also. The mechanical systole, evaluated by phonocardiography, was not correspondingly lengthened.

None of the known causes of prolongation of the Q-T interval could be demonstrated. The blood levels for calcium, phosphorus, and potassium were

all normal, as were also the basal metabolic rate and the glucose tolerance test. The condition is considered to be due to a congenital disorder of the myocardial metabolism, caused by some enzymatic deficiency.

The unusual clinical symptoms, the exceptional electrocardiographic findings, and the serious outcome of the illness, together, represent a characteristic syndrome which to our knowledge has not been described before.

The disorder may be in some cases a possible cause of inexplicable death in children.

We are greatly indebted to Dr. Johan Kloster, Head of the Medical Department of Aust-Agder and Arendal Central Hospital, for his kind assistance in placing informations, electrocardiograms, etc., at our disposal.

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ELECTROCARDIOGRAPHY IN EXPERIMENTAL ATHEROSCLEROSIS AND HYPERTENSION

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THE electrocardiographic observations of animals submitted to an experimental diet of cholesterol are not numerous. Nyboer, Bruger and Rabson[1] studied the electrocardiographic and pathologic alterations of the heart of rabbits subjected to that regimen. They used one series of 12 animals, of which 5 were for control, the period of observation being 126 days. The diet was equal for all, but 3 times a week 1 Gm. of cholesterol was administered to 7 of the rabbits. In the group that took cholesterol the development of marked lesions of atherosclerosis was verified, but neither modifications of the structure of the myocardium nor significant electrocardiographic alterations were found. Above all, no changes of the RS-T segment were encountered, but extrasystoles were noted in animals of the two groups. Wakerlin and associates[2] also did not describe electrocardiographic modifications in dogs.

In an experimental study of the relations between atherosclerosis and hypertension, we were able to observe electrocardiographic tracings in various phases of the development of these processes. Some of the electrocardiograms obtained were remarkably removed from the normal outlines.

METHOD

Various series of rabbits were used, divided into 3 groups:

1. Series CLT—1.5 Gm. of cholesterol was administered daily to the animals of this group.
2. Series P-A—Hypertension was produced in these animals.
3. Series P-B—Hypertension was produced in this group of animals and 1.5 Gm. of cholesterol was administered daily to them. None of the animals was sacrificed, death being spontaneous in all. The hypertension was produced by the method described by Pickering and Prinzmetal,[3] and the reading of the pressure was made by the Grant and Rothschild capsule,[4] according to the indications of the latter authors. Tracings of the classical derivations of the leads, of the unipolar leads, and of the precordial leads V_1, V_3, and V_6 were obtained (Fig. 1).

RESULTS

Series CLT.—

Rabbit 30-A2: After 48 days of administration of cholesterol, the electrocardiogram presented the following modifications (Fig. 2), in relation to the

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normal: The frequency of 300 p.p.m., dropped to less than 200. The duration of the rapid ventricular group passed from 0.02 to 0.06 second. The T wave became negative in D_I and aV_L, the S-T segment depressed in V_3 and V_6. P waves were not found preceding the QRS complex, but it is probable that the notch that was observed in the ascending branch of the T wave corresponded to the implantation of P. It seems that the electrocardiographic characteristics noted can be considered to support inferior nodal rhythm and disturbances of the intraventricular conduction.

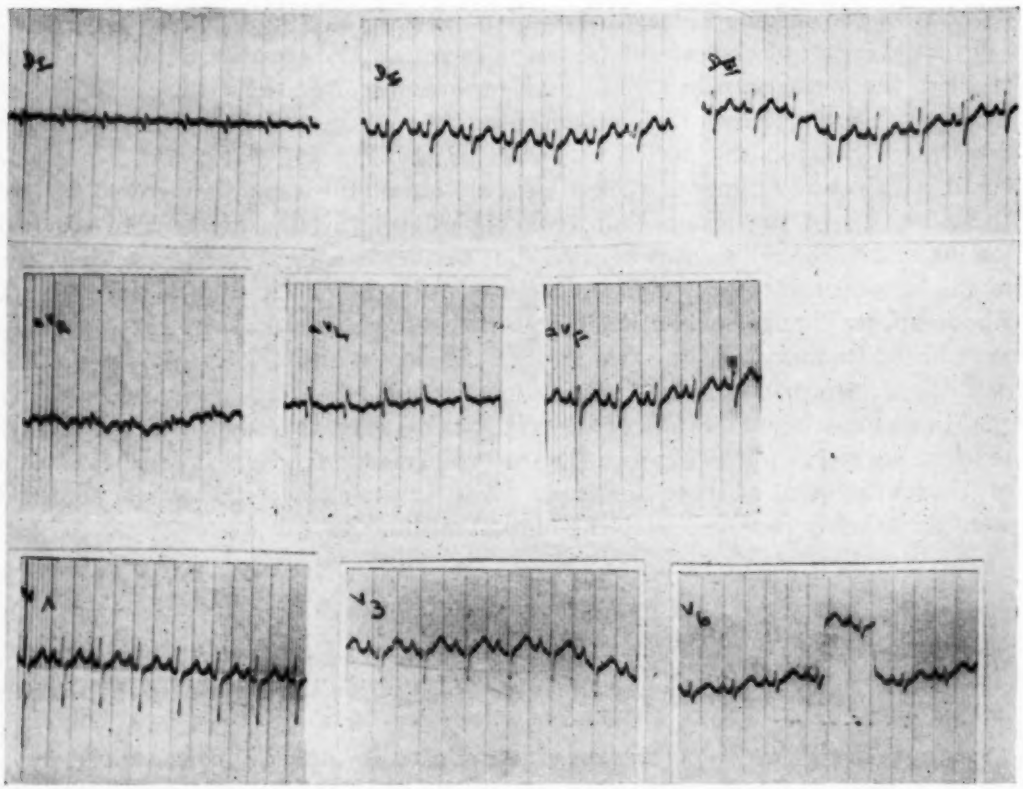

Fig. 1.—Electrocardiogram of a normal rabbit.

Microscopic Examination.—In the myocardium the following changes were found: The small arteries showed accumulations of foam cells in the intima, but rarely completely obliterating the lumen. Rare foci of fibrosis were found, of a slight degree, small, juxtaendocardiac and almost only at the level of the anterolateral wall of the left ventricle, in a cut that passed at the level of the superior part of the septum.

Rabbit Number 7: After 194 days of administration of cholesterol, there was obtained on the day of the animal's death the tracing that is reproduced in Fig. 3, in which the following alterations were found: D_I—slight depression of ST-T, with T negative; D_{II} and D_{III}—the S-T segment strongly convex at the top, originating in the S wave and rounding the T; aV_R—ventricular complexes of the type Qr, with S-T slightly depressed, and T negative; aV_L—rapid

group of greatly reduced voltage, the segment ST-T assuming an aspect similar to that found in aV_R; aV_F—identical to that of D_{II} and D_{III}; V_1—ventricular complexes of the type rS with abnormal elevation of ST-T, of superior convexity; V_3—the characteristics indicated in D_{II}, D_{III}, and aV_F; V_6—complexes of the type Rs, with S-T slightly depressed, and T flat.

Microscopic Examination of the Myocardium.—Marked modifications were found in the subendocardiac zones, principally in the left ventricle, both in the region of the septum and in the left half. The alterations consisted of zones of muscular atrophy, with more or less complete disappearance of the fibers and proliferation of the regional conjunctive elements, whether of the sarcolemma or the interstitial conjunctive tissue. In these foci most of the cells possessed foam cytoplasm and voluminous nuclei, some of them with 2 nuclei. Even in the same foci there was always found a certain proliferation of collagenous fibers, ranging from very slight to very advanced degrees of fibrosis; one of the latter was found at the level of a papillary muscle. The artery that irrigated it presented the lumen almost completely obliterated by accumulations of foam cells.

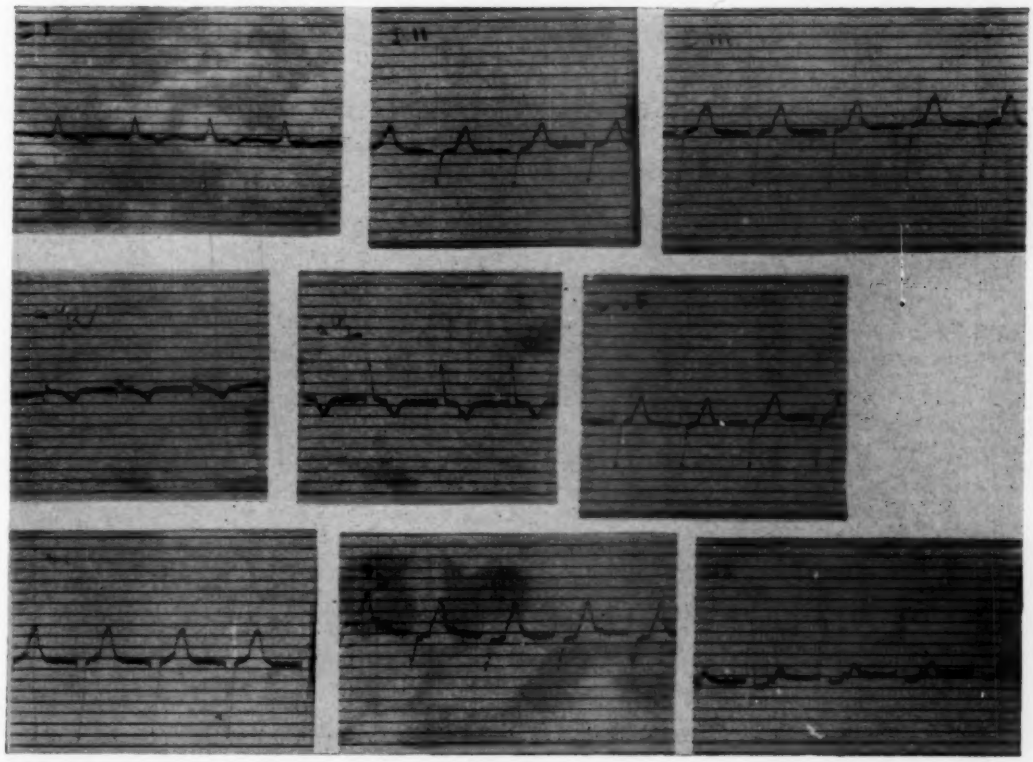

Fig. 2.—Rabbit 30-A2 (Series CLT). Nodal rhythm. Intraventricular conduction disturbance.

Rabbit Number 8: In a tracing obtained 45 days after the administration of cholesterol there was noted a ventricular extrasystole in all the derivations except D_I and D_{II}.

Microscopic Examination of the Myocardium.—There were no alterations of the vessels nor foci of fibrosis. Only a strengthening of the normal reticule between the muscular fibers of the internal zones of the myocardium (left ventricle and septum) was observed, without atrophy or disappearance of the muscular fibers. Besides this, a slight thickening of the subendocardiac

conjunctive tissue was even noticed, more distinct at the level of the left ventricle and the septum. These alterations were observed to be of the same intensity in the papillary muscles.

Series P-A.—In the animals of this set, hypertension was produced and cholesterol was not administered. In 2 of them the following electrocardiographic modifications were obtained:

Rabbit P-A 30: In relation to the first tracing, the following modifications were noticed: IV—(45 days after the placing of the clamp) = R high in V_3 and V_6, and the T wave high and peaked in V_3 and V_6; VII—(60 days after the clamp) = extrasystolic bigeminy and T negative in V_6 (Fig. 4); XII—R high in V_1 and V_3, and T lower than in the IV tracing.

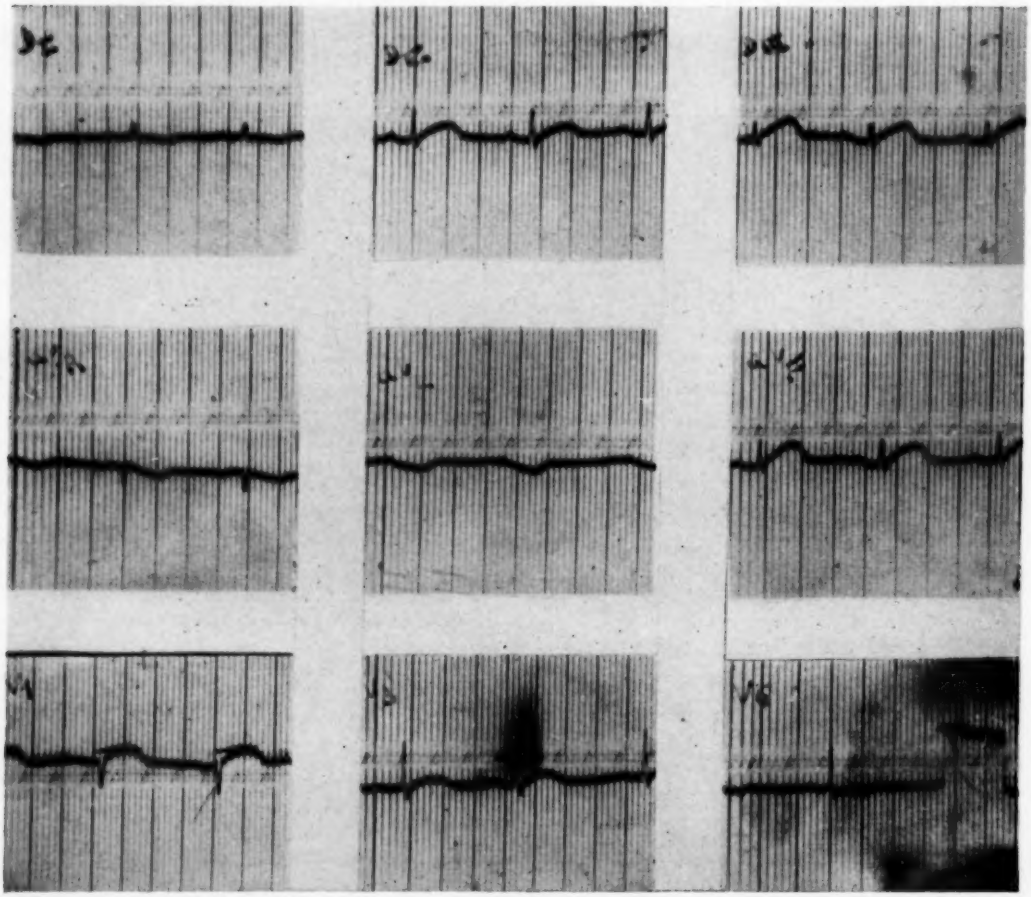

Fig. 3.—Rabbit No. 7 (Series CLT). Changes of the S-T segment.

Rabbit P-A 40: Modifications were found in 2 electrocardiograms, relative to the first: XVII ECG—R waves well marked in D_I, V_3, and V_6, and the T wave became negative in D_I, and V_6 (Fig. 5); XX ECG—The frequency of the pulse, around 300, became less than 100. The S-T was strongly elevated and of monophasic tendency in D_{II}, D_{III}, aV_F, V_3, and V_6, and with the same aspect, but negative, in aV_R and aV_L (Fig. 6).

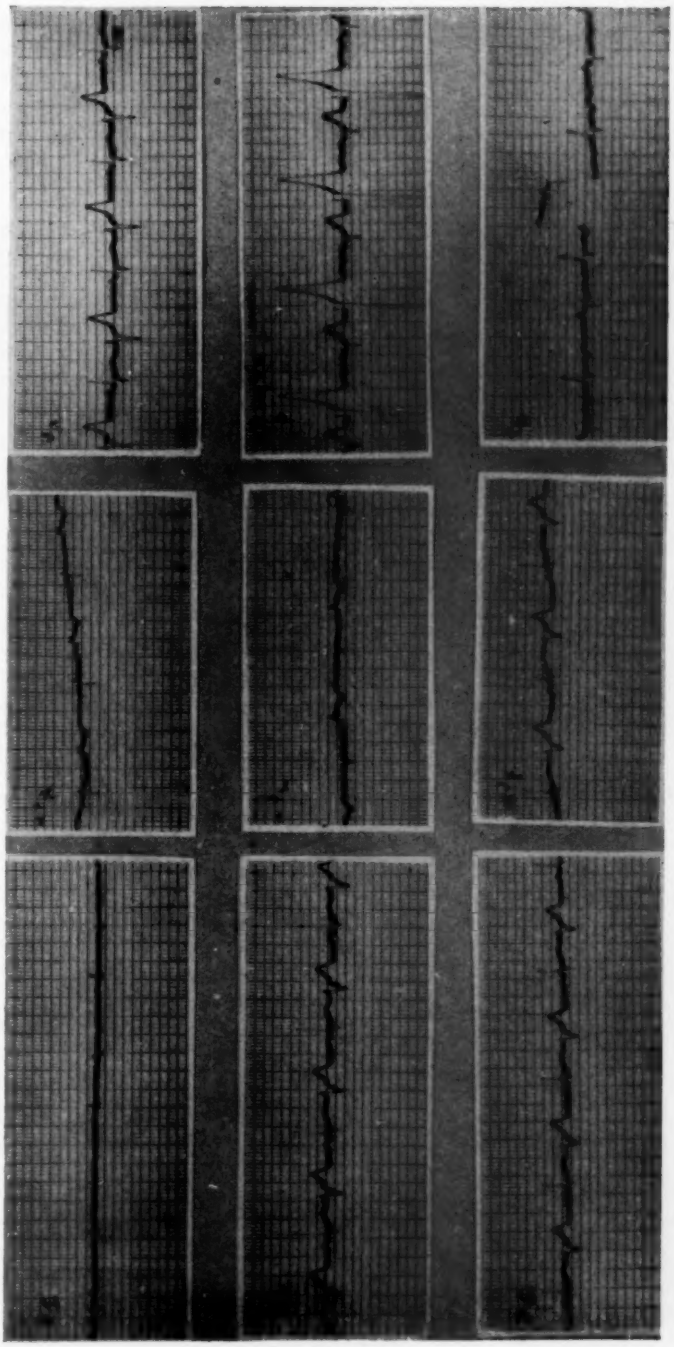

Fig. 4.—Rabbit P-A 30. Extrasystolic bigeminism; T negative in V_6.

These outlines are like a mirror image of the XIV electrocardiogram of Rabbit P-B 28 (Fig. 8).

Microscopic Examination.—An increase of the thickening of the cardiac muscular fiber, when compared with a set of hearts of normal rabbits of identical weight, was noticed. There were no other myocardial alterations, especially such as foci of fibrosis. Several of the coronary vessels, compared with vessels as nearly identical as possible of normal rabbits of the same weight, showed a wall also thicker, at the expense of the increase of the layers of the smooth muscular fibers; the lumen of these vessels was, in consequence, narrower. Not infrequently some were observed in which it was reduced to a slit, in spite of there being no alterations of the intima.

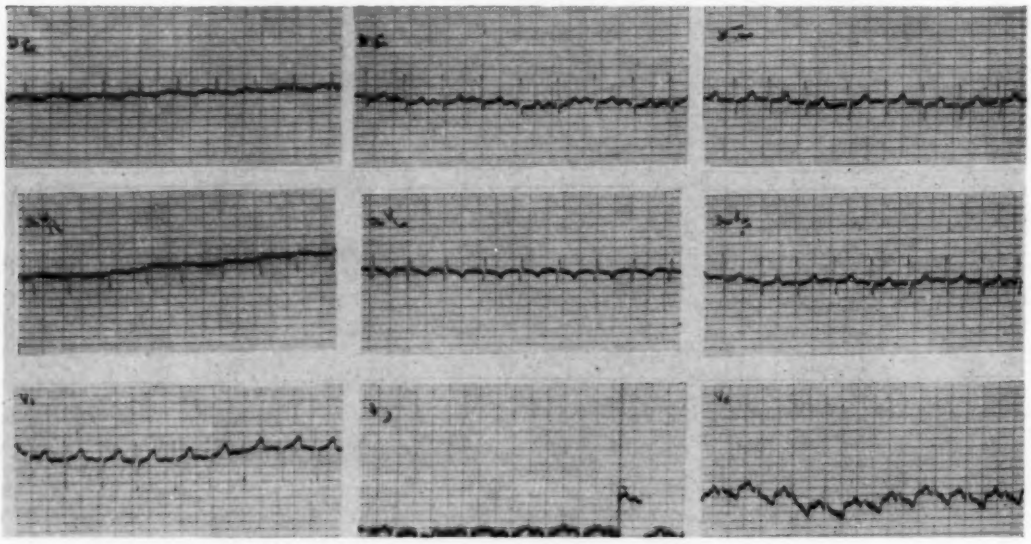

Fig. 5.—Rabbit P-A 40. R well marked in D_I, V_3 and V_6. T negative in D_I and V_6.

Series P-B.—Experimental hypertension was produced in the animals of this set, and 1.5 Gm. of cholesterol was administered daily.

Rabbit P-B 28: The tracings XIII and XIV present the following modifications in relation to the first: XIII (Fig. 7)—R wave of small voltage in D_I and a flat T; the S-T segment slightly depressed with T positive in D_{II} and D_{III}. Of the unipolar leads the derivation aV_F was found to be essentially modified: S-T depressed and T diphasic. In V_1 the R wave became dominant, with S reduced. In V_1 and V_3 was found a rectilinear depression of RS-T with T diphasic; in V_6 this depression was much less marked. XIV (Fig. 8)—In this ECG (the last obtained) the former characteristics were drawn in a remarkable form, resembling the experimental intracardiac curves. The derivations D_{II}, D_{III}, aV_F, V_1, V_3, and V_6 presented complexes of negative monophasic type. In aV_R and aV_L, there was found an abnormal elevation of the segment RS-T, of superior convexity and of monophasic type.

Microscopic Examination.—With the exception of principal coronary branches, all the coronary ramifications, and principally the smallest, contained abundant lipids accumulated in the intima, in the form of big "cushions" that completely obliterated the vascular lumen or reduced it to a minute slit where there was room for only a few erythrocytes. In the Mallory stain it was

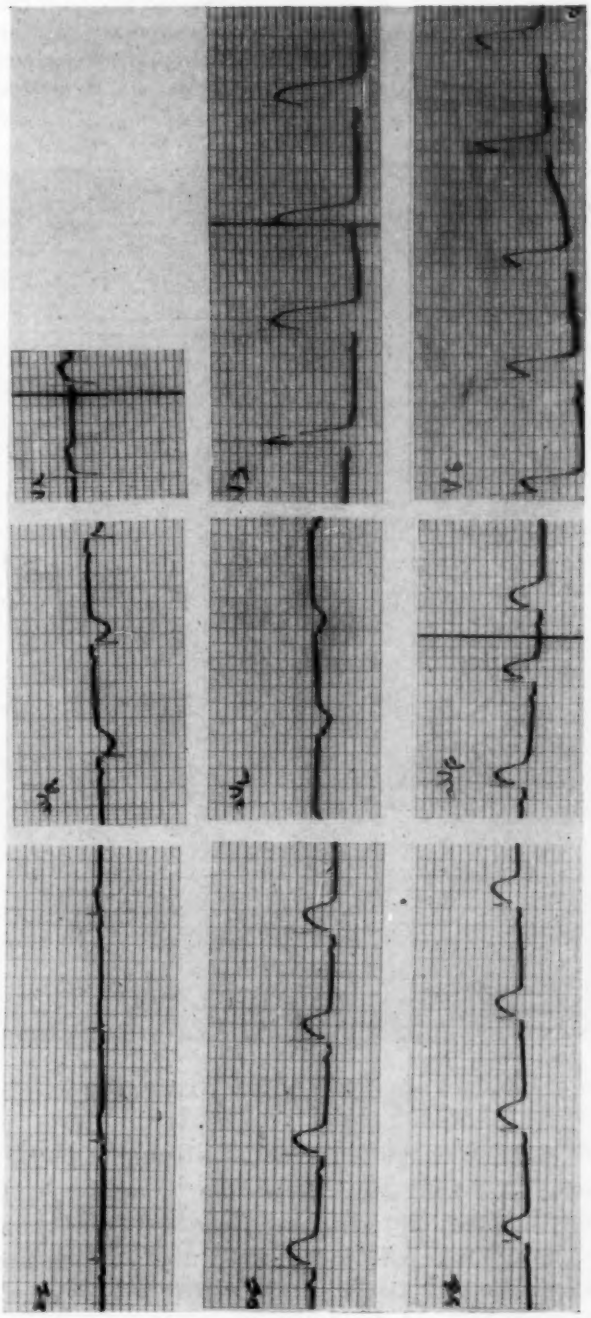

Fig. 6.—The same animal. Bradycardia; S-T of monophasic tendency.

verified that in the thickness of these "cushions" existed a dense reticule of precollagenous and collagenous fibers. Along a relatively broad strip of the myocardium and particularly of the left ventricle and of the septum there existed numerous foci at the level of which the fibrous conjunctive tissue was greatly increased. At its level, the corresponding muscular fibers had completely disappeared or either showed figures or very marked atrophy. On the outside, this proliferation was made in the form of radial strips that as a rule did not pass beyond the interior half of the thickness of the myocardium. These alterations were particularly marked at the level of the fleshy columns of the first row and of the papillary muscles. Fig. 9 corresponds to the scheme of these lesions.

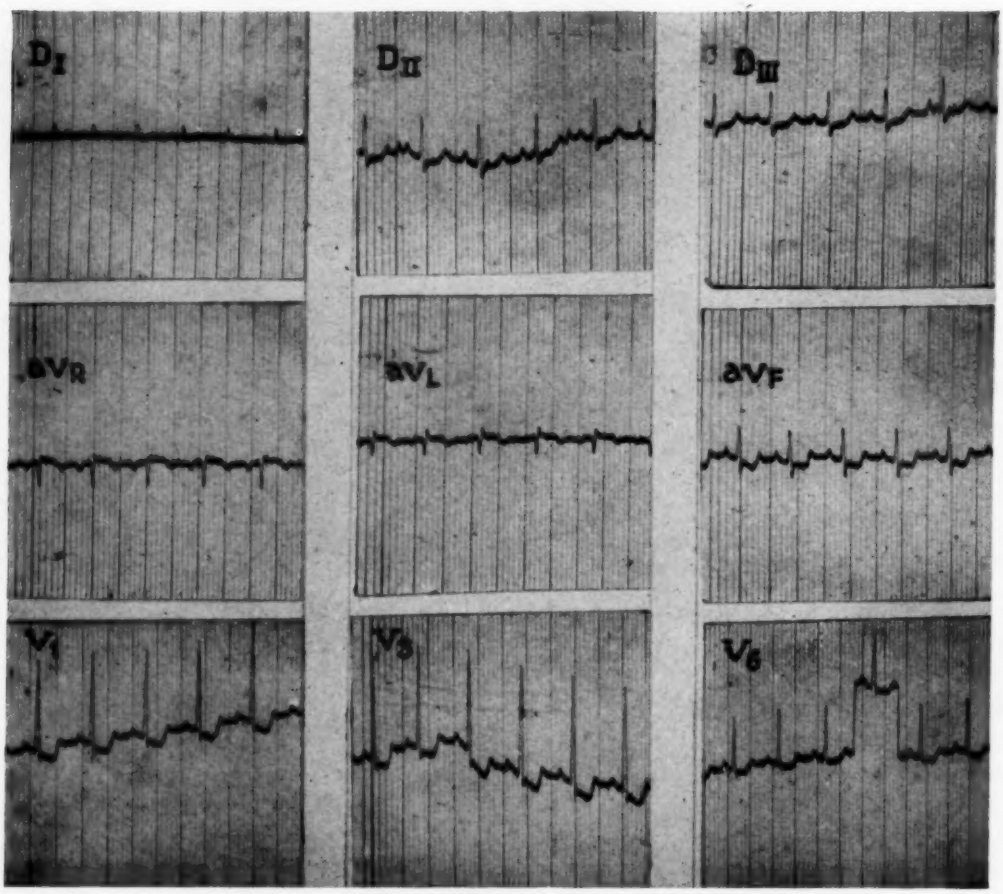

Fig. 7.—Rabbit P-B 28. Changes of the segment S-T.

Rabbit P-B 31: The tracings XIII (Fig. 10) and XIV (Fig. 11) present marked modifications. In tracing XIII the outline of the curve presents a certain similarity to those of the Rabbits P-B 8 and P-B 28 (accentuated bradycardia). In D_{II}, D_{III}, aV_F, V_3, and V_6, S-T is depressed and commences before the inscription of the S wave finishes. In aV_R and aV_L the S-T is elevated. In tracing XIV the alterations described are more accentuated, the S-T segment assuming a monophasic aspect.

Microscopic Examination.—Practically all the vessels showed accumulations of foam cells in the intima, in the form of the usual "cushions," with reduction of the lumens, particularly the

arteries of small and medium size. They were also found in the great ones, although there the "cushions" were rather small. In the internal zones of the myocardium of the left ventricle and of the septum, more in the former and principally at the level of the anterior zones, there were found foci composed of a dense reticule of collagenous fibers at the level of which the muscular fibers were intensely atrophied or had even disappeared. These lesions were very important at the level of the most important fleshy columns and papillary muscles. It was here also that the described vascular lesions were most intense. At the level of the right ventricular face of the septum, these cicatrices did not exist, but at only a few points was there a slight strengthening of the normal fibrillar skeleton.

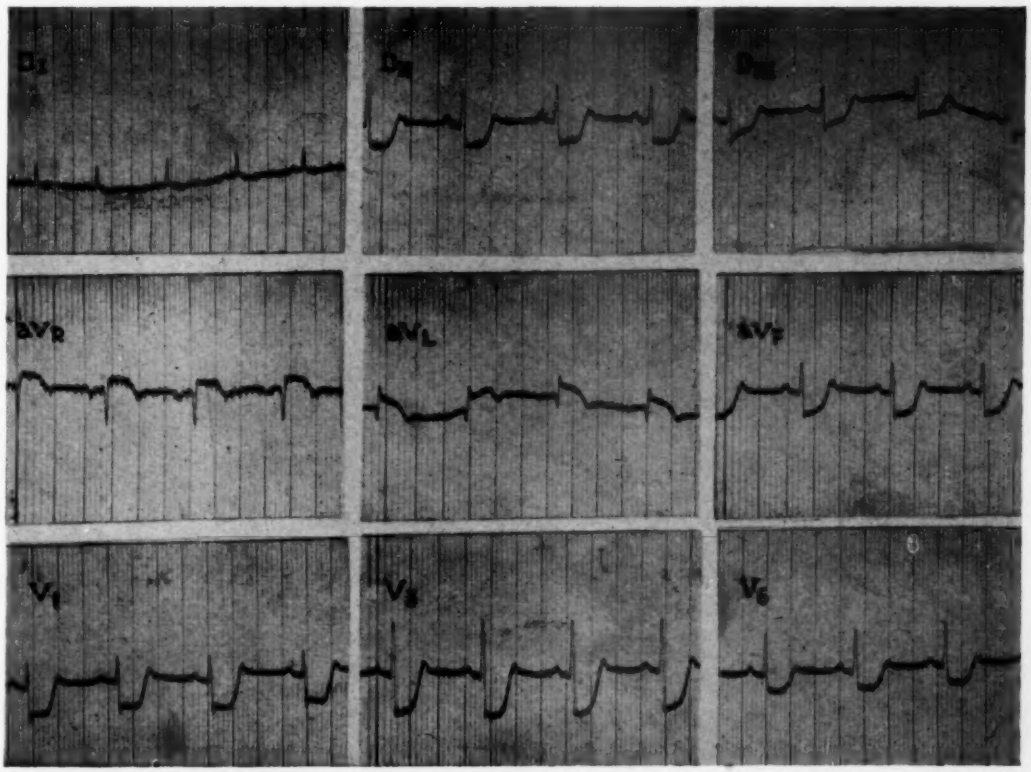

Fig. 8.—The same animal. Complexes of negative monophasic type.

Rabbit P-B 12: Two electrocardiograms show accentuated modifications in the relation to the first: XXIII (Fig. 12) = S-T depressed, of superior convexity, in D_{II}, D_{III}, aV_F, V_3, and V_6. The T wave becomes negative in D_I, D_{II}, aV_F, V_3, and V_6, and diphasic in D_{III}. XXIV (Fig. 13) = Great bradycardia. The QRS complexes show significant alterations: qrS in D_I; QR in aV_R; Qr in aV_L; RS in the others; S-T segments depressed and of superior convexity in D_{II}, D_{III}, aV_F, V_1, V_3, and V_6. At the end of the ST-T segment there appears to be grafted a small wave that records a second P, which could admit the possibility of a reciprocal rhythm.

Microscopic Examination.—Some ramifications of the coronary arteries showed almost total obliteration of the lumen by cushions of the intima. At the level of the left ventricle and princi-

pally along a subendocardial strip, foci of fibrosis existed. In 2 papillary muscles there was necrosis of the muscle fibers and interstitial fibrosis.

Rabbit P-B 8: Of this animal we possess only tracings with the classical derivations and the unipolar leads. Three electrocardiograms show alterations: X (Fig. 14).—In D_I the QRS complexes assume the well-defined outline of the qR, type, S-T segment of superior convexity and T negative; Similar characteristics are found in aV_L. XIII (Fig. 15).—The frequency fell from around 300 to 100 p.p.m., with S-T depressed in D_{II}, D_{III}, aV_F, and elevated in aV_R and aV_L. These aspects are similar to those observed in Rabbit P-B 28 (Fig. 8). XIV (Fig. 16).—Very great bradycardia. The depression of S-T was substituted by abnormal elevation.

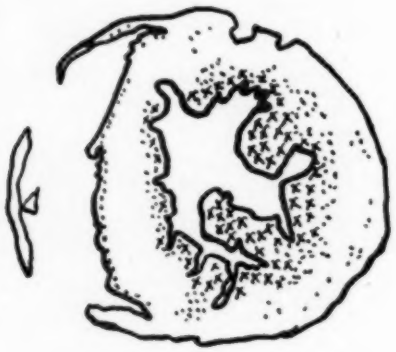

Fig. 9.—The same rabbit. Scheme of the lesions

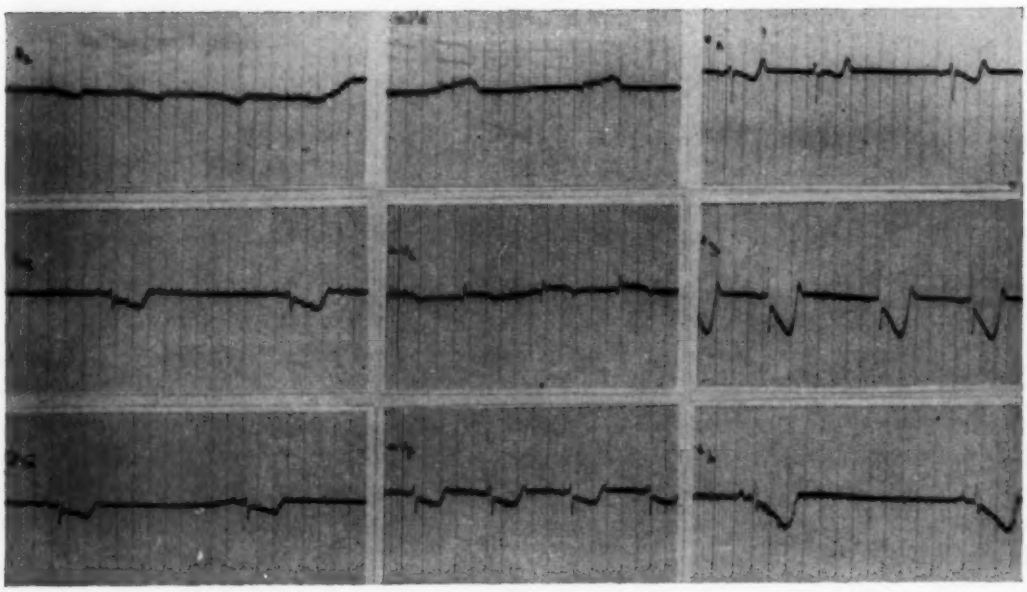

Fig. 10.—Rabbit P-B 31. Bradycardia; S-T depressed.

COMMENTS

The electrocardiographic tracings reproduced show that in any of the sets of animals used in this work curves with alterations were obtained.

1. In the animals subjected to the administration of cholesterol, modifications of the electrocardiograms of those animals that also had hypertension (Series P-B) were found with greater frequency. In the series that was subjected only to the administration of cholesterol, the tracing of Rabbit 30-A2 is fairly well modified and yet the degree of myocardiac fibrosis developed was slight. The tracing of Rabbit P-B 28 (Fig. 8) resembles the intracardiac curves obtained by

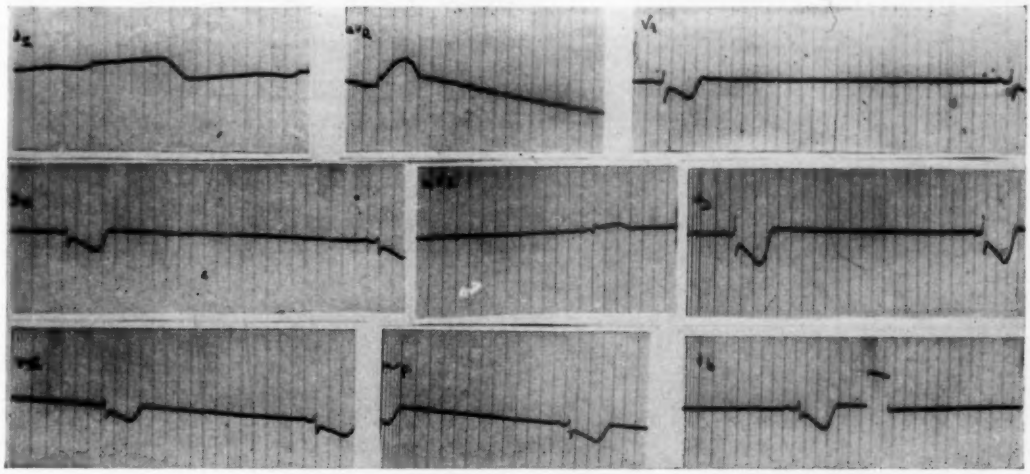

Fig. 11.—The same animal. Accentuation of the changes shown.

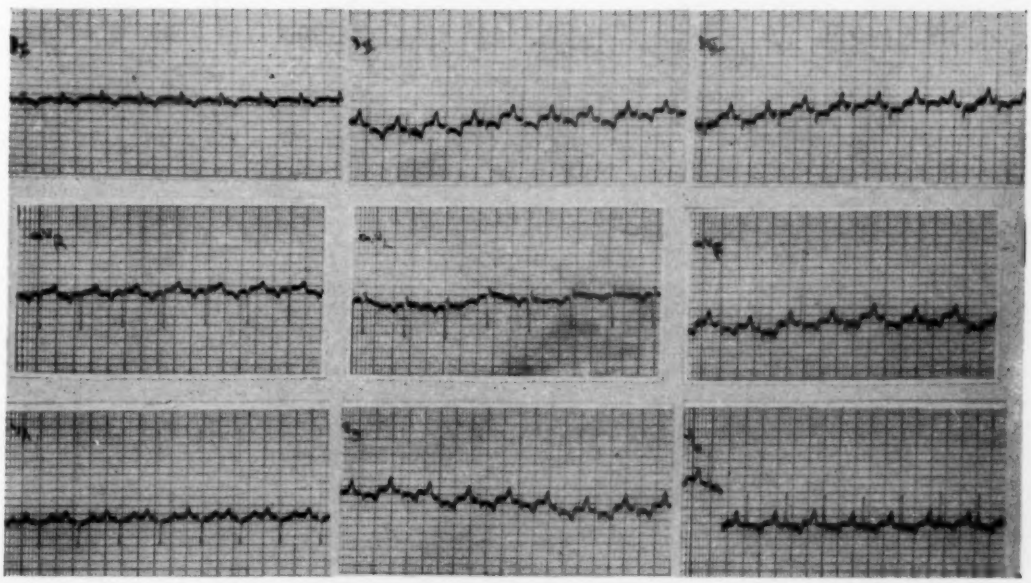

Fig. 12.—Rabbit P-B 12. Changes of the segment ST-T.

Sodi-Pallares, who succeeded in registering the potentialities of the epicardiac surface of the left ventricle, after accidental subendocardiac lesion produced by the introduction of an electrode into the interior of that cavity.[5] The curves thus obtained on the anterior face of the heart showed a negative monophasic complex (in a direction opposite from those obtained in the interior of the cavity) with the characteristics almost identical to those of the tracings of Rabbit P-B 28. Whether in the case of Sodi-Pallares or in ours, the lesions corresponded in the

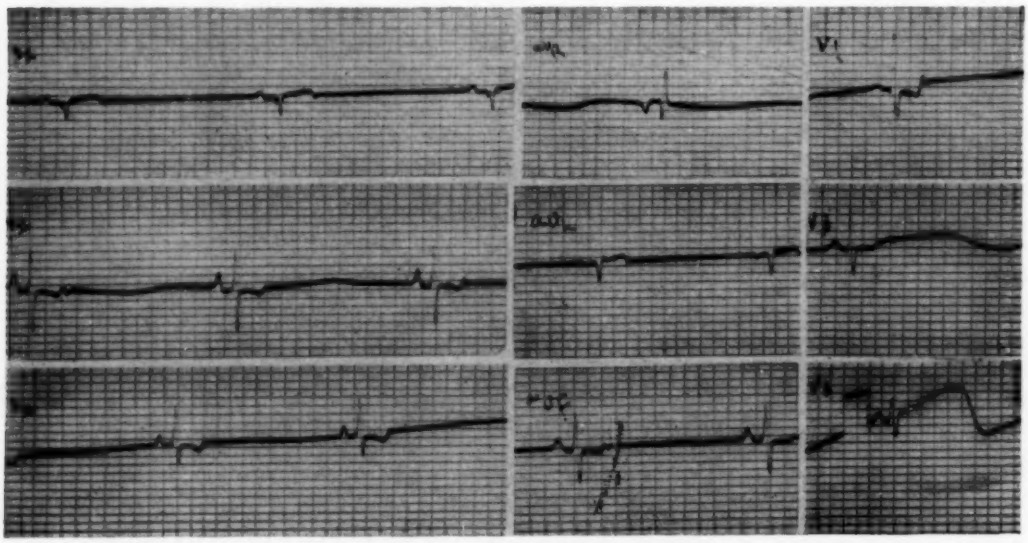

Fig. 13.—The same animal. Changes of the QRS and ST-T. Bradycardia.

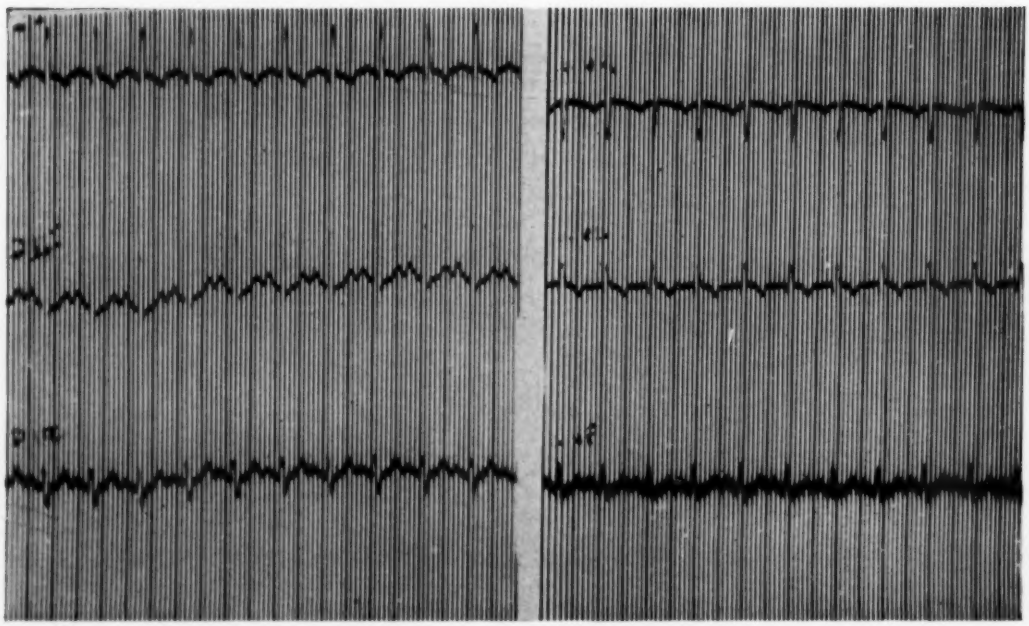

Fig. 14.—Rabbit P-B 8. S-T of superior convexity and T negative in D_I and aV_L.

subendocardial localization, those of P-B 28 being due to the administration of cholesterol. Both in this animal and in P-B 31, the administration of cholesterol was begun only some months after the placing of the clamp. On the contrary, in P-B 12 the cholesterol was started immediately following the placing of the clamp. The tracing XXIII of this rabbit (Fig. 12) shows the aspects usually found in left ventricular strain of human hypertension. Tracing XXIV (Fig. 13) was taken some minutes before the death of the animal. Also, the electrocardiogram XIV of P-B 8 (Fig. 16) was obtained on the day on which the animal died. The electrocardiograms of Rabbits P-B 8, P-B 28, and P-B 31 assume common characteristics, there being noted on the microscopic examination of each of them the existence of an extensive subendocardial fibrosis (Figs. 15, 8, 10).

2. Of the animals in which hypertension was produced and to which cholesterol was not administered, the electrocardiograms of Rabbit P-A 40 (Fig. 5) must be emphasized and must be compared with the tracing of Fig. 12

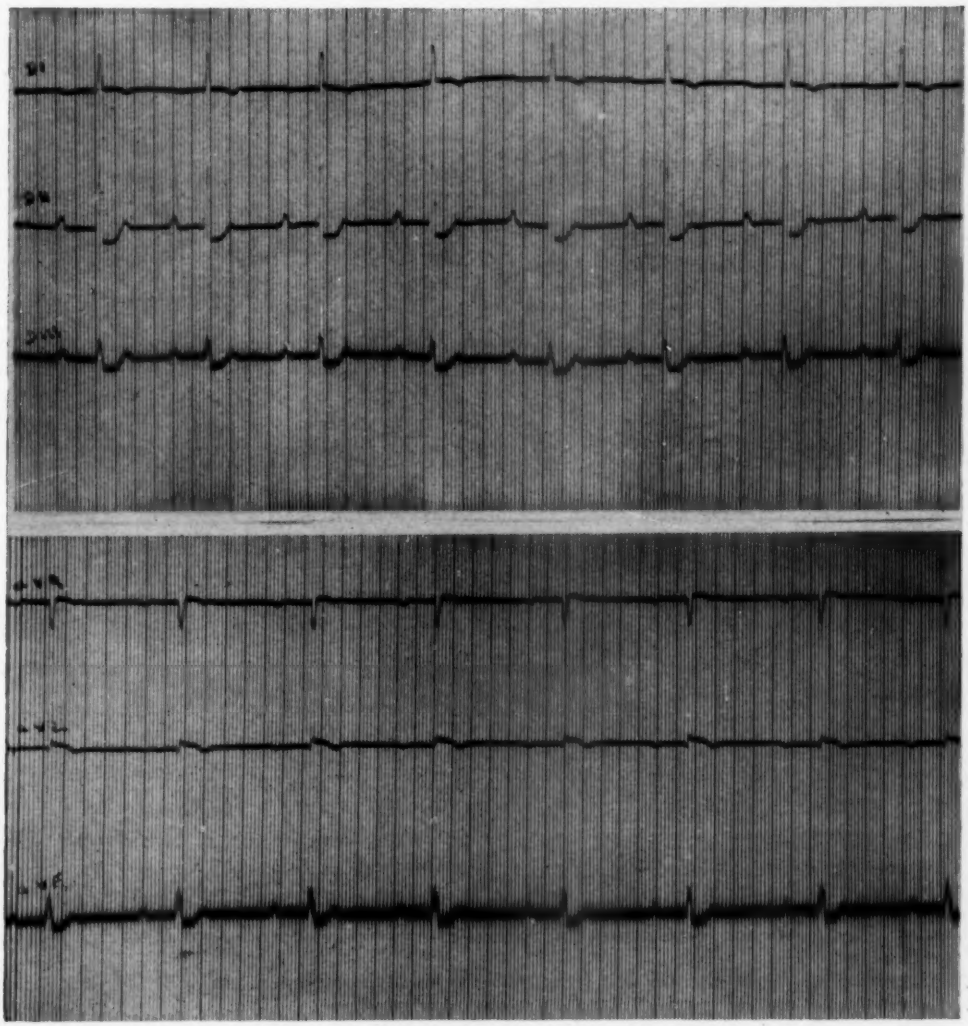

Fig. 15.—The same animal. Bradycardia. S-T depressed in D_{II}, D_{III}, aV_F, and elevated in aV_R and aV_L.

referring to P-B 12. The outlines of the S-T segment and of the T wave in this latter are much more clearly defined, which could be attributed to the subendocardial fibrosis which the administration of cholesterol produced, through atheromatous lesions of the coronaries.

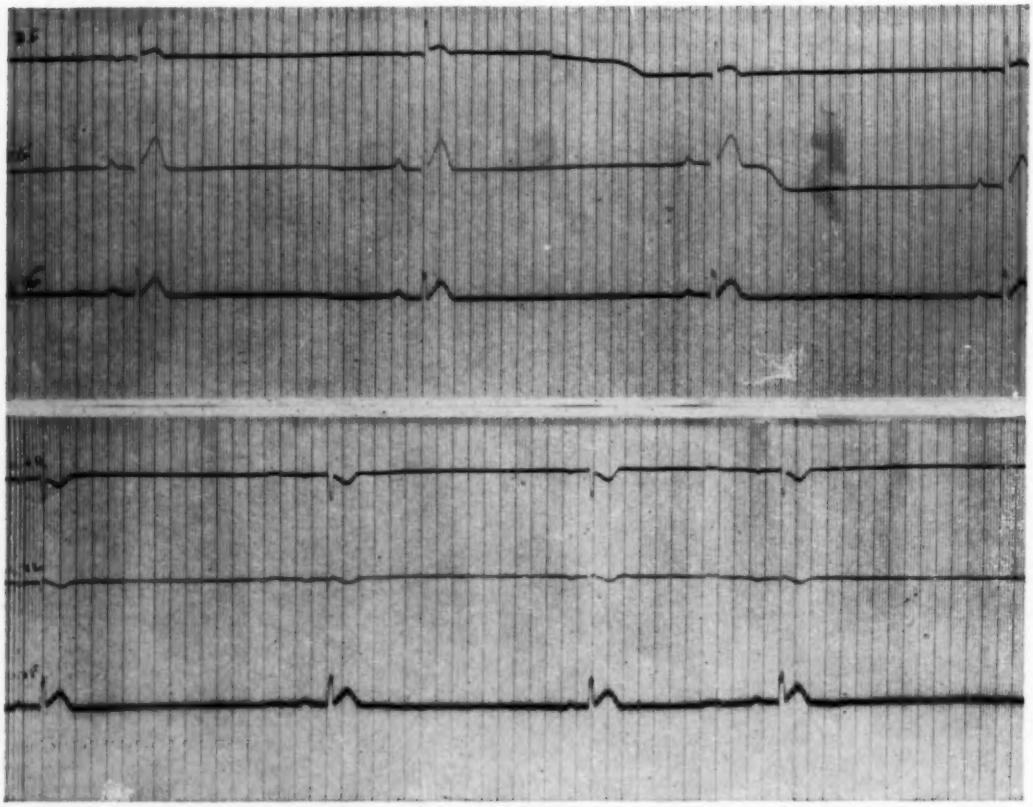

Fig. 16.—The same rabbit. Abnormal elevation of the S-T segment.

SUMMARY

The electrocardiograms obtained in 3 sets of rabbits subjected to different experimental conditions are reproduced: (a) daily administration of cholesterol; (b) hypertension; (c) hypertension and administration of cholesterol.

We thank Dr. Demetrio Sodi-Pallares for his kindly and valuable teaching on the electrocardiograms here published.

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THE BURGER TRIANGLE IN CURVE FORM

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ONE important recent advancement in vectorcardiography is the Burger triangle.[1] Burger and associates introduced into vectorcardiography the concept of lead vector, which is the quotient of lead deflection and heart vector. On this basis they constructed from experimental data a nonequilateral triangle, which gives accurate results of heart vectors in the RLF plane, even though the human thorax is irregular in shape, tissue conductivity is heterogeneous, and heart vector is eccentric. Burger disproved the Einthoven assumption and obtained his triangle by accurate measurements.

In the history of the Einthoven triangle, aside from several debates concerning its validity, some diagrams have been derived. Among them may be mentioned the charts of Carter and associates[2] and Dieuaide,[3] the triaxial reference system of Bayley,[4] the hexaxial reference system of Sodi-Pallares and associates,[5] and recently the polarity circle system of Zao and associates.[6] They are useful in clinical routine, but none of them is accurate.

Burger's first paper on his triangle was published in 1946. Since his papers are very short and not easily understood by physicians, his triangle has been slow to gain recognition. Other investigators have explained the Burger triangle in nontechnical terms,[7] or with simple mathematics.[8] The simplification of the use of the Burger triangle was proposed,[7] and was confirmed in subsequent experimental study.[9]

This paper describes the Burger triangle in curve form. It is easy to use, and it can be used together with the Einthoven triangle in curve form[10] to obtain simultaneous results from both triangles.

DESCRIPTION AND USE

At the two vertical borders (Fig. 1) there are indicated quotients of corresponding deflections written in limb Leads I and III (each scale mark = 0.04). At the two horizontal borders there are indicated directions in degrees for the RLF plane (each scale mark = two degrees). The two curves correlate quotients and directions.

This form may be used to determine in the RLF plane any heart vector direction (P, QRS, ST, T), whether mean, main, or instantaneous.

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Let e_1 = any deflection in Lead I, mean, main, or instantaneous.
e_3 = corresponding deflection in Lead III.

The procedure is as follows:

1. Measure e_1 and e_3. Calculate the quotient e_1/e_3.
2. Use the bottom horizontal border if Lead I is positive, the top

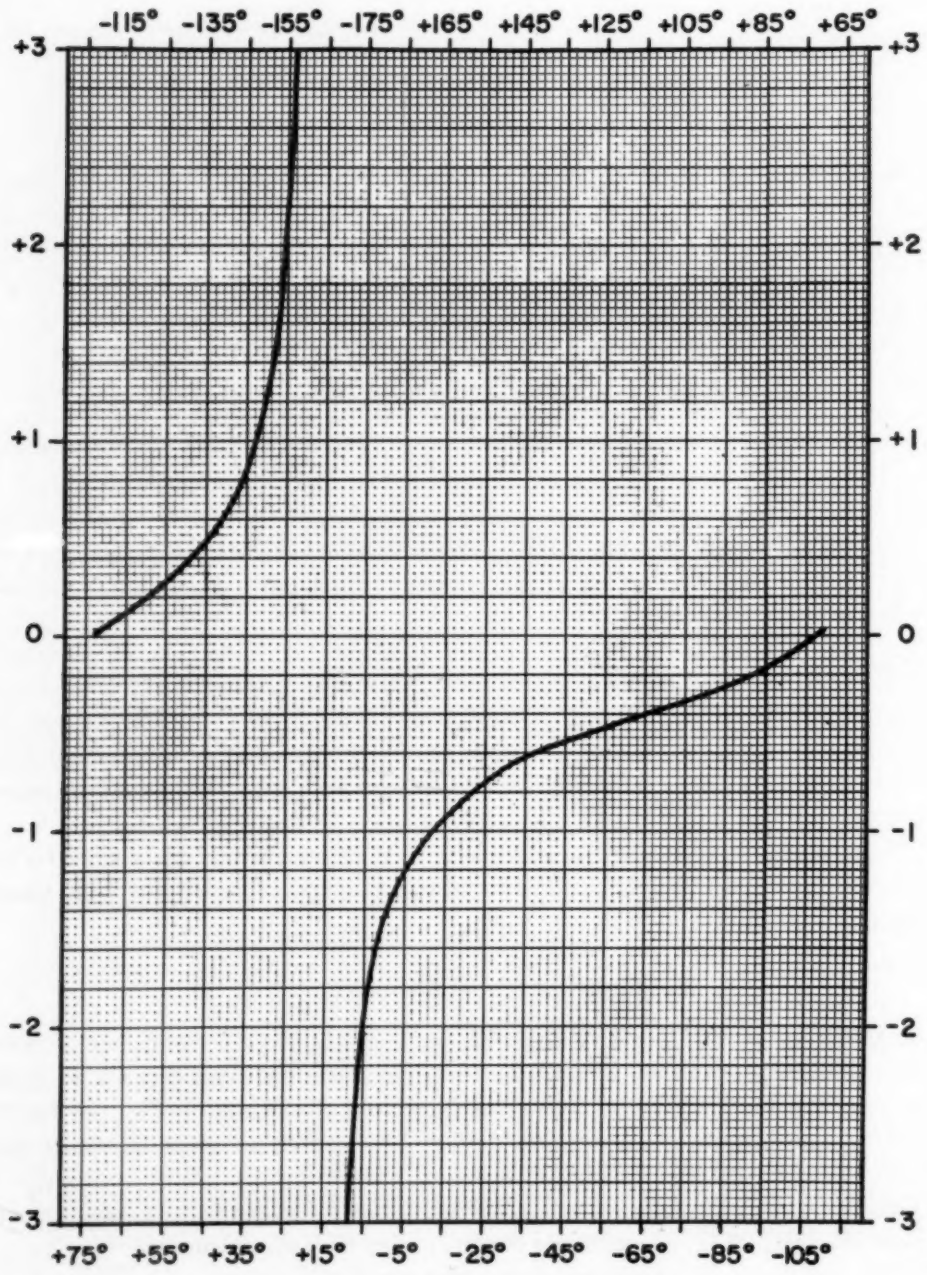

Fig. 1.—The Burger triangle in curve form.

horizontal border if Lead I is negative. The curve correlates the quotient to the direction.

3. Exceptionally the quotient is zero or larger than ∓ 3. If it is zero, the direction is $+72°$ when e_3 is positive, and $-108°$ when e_3 is negative. If it is larger than ∓ 3, use Table I. If it is infinite, the direction is $+16°$ when e_1 is positive, and $-164°$ when e_1 is negative.

Example: To find ÂQRS if AQRS is +5 Ashman units in Leads I and III, $e_1/e_3 = +1$.
Since e_1 is positive, the direction indicated at bottom horizontal border corresponding +1 is +33°.

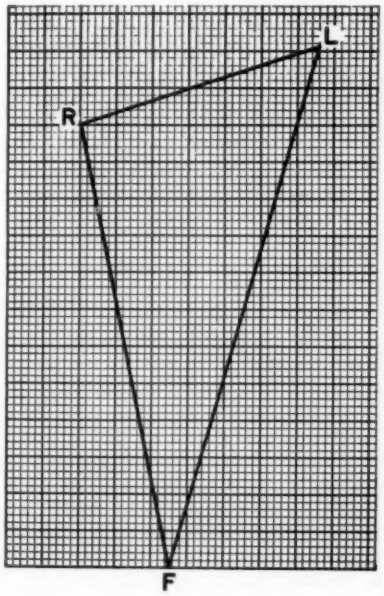

Fig. 2A

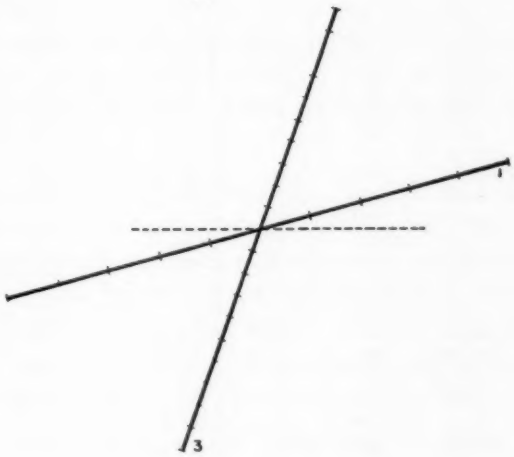

Fig. 2B

Fig. 2A.—The Burger triangle.

Fig. 2B.—The biaxial figure of Lead vector I and Lead vector III. The dashed line represents the horizon. This figure can be used just as the Bayley triaxial figure is used and on the average gives more accurate results than the latter.

CONSTRUCTION

The positive direction and length of Lead vectors I and III of the Burger triangle* (Fig. 2*A*) are as follows:

	Positive direction	*Length*
Lead vector I	−18°	6.9 cm.
Lead vector III	+106°	15.0 cm.

According to Brody[11] lead vectors may be used as lead axes to plot heart vectors if each of the former is divided so that each division is inversely pro-

*The receipt of the original, average triangle from Dr. H. C. Burger, Utrecht, is gratefully acknowledged.

portional to the corresponding lead vector length. After a very elementary calculation we found the division of Lead vector I to Lead vector III is as 2.2 to 1.

Fig. 2*B* shows a biaxial reference figure of Lead vectors I and III with above divisions and directions.[12] A heart vector of 10 cm. in length originating from its intersection was rotated around the RLF plane. At each 5° interval the orthogonal projection on Lead vectors I and III were measured, from which the quotient e_1/e_3 was calculated. The results are given in Table I.

TABLE I

RLF PLANE DIRECTIONS	LEAD VECTOR I DIVISIONS	LEAD VECTOR III DIVISIONS	QUOTIENT e_1/e_3
0° ∓180°	4.32 (+ −)	2.7 (− +)	−1.60
+5° −175°	4.19 (+ −)	1.88 (− +)	−2.23
+10° −170°	4.01 (+ −)	1.0 (− +)	−4.01
+15° −165°	3.80 (+ −)	0.18 (− +)	−21.11
+20° −160°	3.57 (+ −)	0.75 (+ −)	+4.76
+25° −155°	3.31 (+ −)	1.58 (+ −)	+2.10
+30° −150°	3.03 (+ −)	2.43 (+ −)	+1.25
+35° −145°	2.72 (+ −)	3.3 (+ −)	+0.82
+40° −140°	2.40 (+ −)	4.1 (+ −)	+0.59
+45° −135°	2.06 (+ −)	4.88 (+ −)	+0.42
+50° −130°	1.69 (+ −)	5.6 (+ −)	+0.30
+55° −125°	1.33 (+ −)	6.23 (+ −)	+0.21
+60° −120°	0.95 (+ −)	6.9 (+ −)	+0.14
+65° −115°	0.56 (+ −)	7.5 (+ −)	+0.08
+70° −110°	0.17 (+ −)	8.05 (+ −)	+0.02
+75° −105°	0.24 (− +)	8.55 (+ −)	−0.03
+80° −100°	0.64 (− +)	9.0 (+ −)	−0.07
+85° −95°	1.01 (− +)	9.3 (+ −)	−0.11
+90° −90°	1.41 (− +)	9.6 (+ −)	−0.15
+95° −85°	1.77 (− +)	9.8 (+ −)	−0.18
+100° −80°	2.13 (− +)	9.93 (+ −)	−0.21
+105° −75°	2.45 (− +)	10.0 (+ −)	−0.25
+110° −70°	2.79 (− +)	9.98 (+ −)	−0.28
+115° −65°	3.09 (− +)	9.88 (+ −)	−0.31
+120° −60°	3.36 (− +)	9.7 (+ −)	−0.35
+125° −55°	3.61 (− +)	9.43 (+ −)	−0.38
+130° −50°	3.84 (− +)	9.1 (+ −)	−0.42
+135° −45°	4.05 (− +)	8.75 (+ −)	−0.46
+140° −40°	4.20 (− +)	8.3 (+ −)	−0.51
+145° −35°	4.34 (− +)	7.8 (+ −)	−0.56
+150° −30°	4.45 (− +)	7.2 (+ −)	−0.62
+155° −25°	4.52 (− +)	6.6 (+ −)	−0.68
+160° −20°	4.55 (− +)	5.88 (+ −)	−0.77
+165° −15°	4.54 (− +)	5.15 (+ −)	−0.88
+170° −10°	4.51 (− +)	4.38 (+ −)	−1.03
+175° −5°	4.43 (− +)	3.58 (+ −)	−1.24

In each parenthesis the first polarity corresponds the RLF plane direction listed in the first vertical column, the second the second vertical column.

DISCUSSION

The Einthoven triangle does not give accurate results, because his assumption is not consistent with reality. By means of an electrolytic model there was demonstrated quantitatively the inaccuracy of the Einthoven triangle as

influenced by heart vector eccentricity and length.[8] The inaccuracy of the Einthoven triangle can be correlated with the shapes of the Burger triangle. The Einthoven triangle is inaccurate for subjects possessing Burger triangles either of isosceles or scalene shape. The more the triangle departs from the equilateral, the more the heart vector direction, calculated in the Einthoven triangle, deviates from the true one.[13]

The Burger triangle was constructed upon accurate experimental data. Its sides (or lead vectors) are determined by real conditions, such as human thorax form, tissue heterogeneity, and heart vector eccentricity. The Burger triangle gives obviously accurate results. However, the migration of the heart vector and the large effective size of the cluster of individual heart vectors may cause the average Burger triangle to be inaccurate. The former situation is encountered in bundle branch block[14] and in premature beats,[15] the latter in precordial leads.[16] In animal experiments it was shown that if an average Burger triangle was used for dextrocardia, results were even more inaccurate than those obtained in the Einthoven triangle.[9] Despite these facts it may be said with certainty that on the average the Burger triangle gives more accurate results than the Einthoven triangle.

Some workers attempt to obtain accurate results from the Einthoven triangle by means of laborious procedure. They measure with great care the enclosed areas under a magnifying glass or cut down enlarged ones by weighing them on a precise balance. In fact, they do not get accurate results. It was shown elsewhere that the simple inspection method based on the Einthoven assumption could give even more accurate results than the above laborious procedure.[17] We shall not go further into this.

The Einthoven triangle may be transformed in curve form,[10] thus from each quotient e_1/e_3 the ECG analyst may obtain simultaneous results of the Burger triangle and of the Einthoven triangle. The inaccuracy of the Einthoven triangle may be checked each time in individual patients without further effort.

In extension of the lead vector concept in space, Burger and associates proposed a nonequilateral tetrahedron.[1] The nonequilateral triangle is more accurate than the equilateral triangle of Einthoven; at the same time the nonequilateral tetrahedron is more accurate than the equilateral tetrahedron of Wilson.[18]

SUMMARY

The average Burger triangle gives more accurate results than the Einthoven triangle. This paper described the average Burger triangle in curve form. It is easier to use than the triangle itself. It was pointed out that the curves may be used together with the curves derived from the Einthoven triangle to obtain simultaneous results from both triangles. The physician may check each time at a glance the inaccuracy of the Einthoven triangle in individual electrocardiograms.

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THE SCALAR PRESENTATION OF ORTHOGONAL LEADS

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RECENTLY, several different reference frames,[1-3] formed by leads constructed in accordance with the concept of the image surface,[4] have been described for use in spatial vectorcardiography. The advocates of these frames have attempted to develop 3 vectorcardiographic leads which are mutually perpendicular, i.e., orthogonal, and which are relatively insensitive to migration of the location of the "electrical center" of the heart during the cardiac cycle.[5-7] The frame suggested by the author[3] has the additional advantage of consisting of 3 leads which intrinsically are of approximately equal magnitude. In the other two systems[1, 2] equality of lead magnitude must be obtained by adjusting the lengths of the 3 leads by amplification or attenuation.

When 3 orthogonal leads are recorded successively as scalar tracings, information concerning the temporal relationships between simultaneously occurring spatial electromotive forces of the heart is not obtainable. Such information can be obtained from *simultaneously* recorded scalar orthogonal leads but only with the extremely laborious plotting of a large number of points spatially. Cathode-ray presentation of two-dimensional vectorcardiographic projections, recorded in either 2 or 3 planes, yields only an incomplete resolution of temporal relationships, since, even if the laborious construction of spatial models is undertaken, the initial and terminal portions of planar QRS loops are usually too indistinct to permit completely accurate synchronization of simultaneously occurring events in the separate planes. The stereovectorcardiogram[1] would seem to be the ideal method of presenting spatial electromotive forces, but it is necessarily limited in its clinical application by the relative expense and complexity of the equipment necessary and by the inability of some individuals to fuse 2 planar vectorcardiographic loops into a single stereoscopic loop.

The present communication describes a method of recording 3 orthogonal leads of equal magnitude singly and in all possible simple combinations, with the result that 13 separate leads, each with a distinctive spatial axis, are quickly and easily obtainable. Thirteen such leads, re-

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corded with the reference frame* recently described by the author,[3] from a patient whose routine clinical electrocardiogram is shown in Fig. 1, are depicted in Fig. 2. For convenience, the leads are numbered 1 to 13 in sequence. The spatial axes of these leads are represented as protruding from the center of a sphere; their angular positions may, therefore, be defined in terms of azimuth (ϕ) and altitude (θ). The 0° point of the former is located at the positive end of the transverse or x axis. Azimuth is measured in a clockwise direction from this point, the observer viewing the transverse or xz plane from above. The positive end of the sagittal or z axis then has an azimuth of +90°. Altitude is measured from the transverse plane which has an altitude of 0°, the lower pole (i.e., the positive end of the longitudinal or y axis) having an altitude of +90° and the upper pole an altitude of −90°. This notation, which is identical to that used by Milnor, Talbot and Newman,[8] is clearly illustrated in Fig. 5 of their article.

In Table I the azimuth and altitude of each of the 13 leads are given in the second and third columns. In the fourth column the leads are designated by the terminology used in the paper[3] describing the details of the vectorcardiographic lead system. Leads +X, +Y, and +Z represent the transverse, longitudinal, and sagittal orthogonal leads, respectively; the plus signs indicate that these leads have their usual polarity and the minus signs indicate a reversal of polarity. In the fifth column the potential difference of each lead is indicated symbolically where E and E′ refer respectively to the potential of the positive and negative electrodes of a lead, and the subscripts x, y, and z designate the respective orthogonal lead. In the sixth column are listed the amplification factors necessary to equalize the magnitudes of all 13 leads. (These factors may be derived simply from geometric considerations.)

Leads 6, 8, and 13 represent the 3 orthogonal leads recorded singly. Leads 2, 4, 5, 7, 10, and 12 represent the 6 possible paired combinations of the 3 orthogonal leads. Leads 1, 3, 9, and 11 represent the 4 possible triple combinations of these leads.

The 13 leads are mounted in Fig. 2 in such a manner that their interrelationships are readily discernable. The reader may easily visualize the contours of the reciprocals of these leads so that, in effect, a total of 26 leads are available, although only 13 need be recorded. In contrast to the present-day 12 lead clinical electrocardiogram which records leads on only 2 approximate planes, frontal and transverse, and to the cathode-ray vectorcardiogram which displays loops on 3 planes, frontal, sagittal, and transverse, the various leads illustrated in Fig. 2, together with their reciprocals designated by minus signs, may be grouped about 9 separate planes. Thus the frontal plane consists of Lead 8 at 0°; Lead 12 at +45°; Lead 13 at +90°; Lead −4 at +135°; Lead −8 at ±180°; Lead −12 at +225° or −135°; Lead −13 at +270° or −90°; and Lead 4 at +315° or −45°. The sagittal plane, viewed from the right,[9] consists of Lead 6 at 0°; Lead 10 at +45°; Lead 13 at +90°; Lead −2 at +135°; Lead −6 at ±180°; Lead −10 at +225° or −135°; Lead −13 at +270° or −90°; and Lead 2 at +315° or −45°. The transverse plane, viewed from above,[9] consists of Lead 8 at 0°; Lead 7 at +45°; Lead 6 at +90°; Lead 5 at +135°; Lead −8 at ±180°; Lead −7 at +225° or −135°; Lead −6 at +270° or −90°; and Lead −5 at +315° or −45°. The general arrangement of the lead axes in these 3 planes is depicted in Fig. 3,*A*. In addition to the 3 conventional planes, there are 6 additional "oblique" planes. Orthogonal Lead 13 is mounted in a long strip, not only to aid in the elucidation of arrhythmias but also to indicate

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*The reference frame utilizes the following 3 leads: (1) Lead X (transverse lead) is formed by a limb-type electrode applied midway between the right anterior axillary and right midaxillary line at the level where the fifth intercostal space intersects the parasternal lines, and a square saline-containing sponge electrode which centers at this same transverse level and extends from the left mid-clavicular line to the left posterior axillary line. (2) Lead Z (sagittal lead) consists of a limb-type electrode placed midway between the vertebral and the left scapular lines at a transverse level approximately 1 cm. caudad to the level of the limb electrode of Lead X, and a square saline-containing sponge electrode centered at the same transverse level as the sponge electrode of Lead X and extending from (but not quite in contact with) the anterior margin of the latter electrode to a symmetrically identical vertical line on the right anterior chest. (3) Lead Y (longitudinal lead) is formed by a limb-type electrode placed on the neck or head, and a network of two similar electrodes, one placed at any convenient location on the left leg, and one placed on the same vertical line upon which the back electrode of Lead Z is located, where such a line intersects a transverse line delineated by the lower margins of the sponge electrodes. For practical purposes the back electrode may be eliminated and Lead Y may be recorded simply as the difference in potential between the left leg and the neck. The left, inferior, and anterior ends of Leads X, Y, and Z, respectively, are assigned a positive polarity.[9]

its inclusion in all 4 of the planes represented by the 4 columns of leads in Fig. 2. Thus Leads 1, 5, 9, and 13 together with their reciprocals and, likewise, Leads 3, 7, 11, and 13, together with their reciprocals, each lie on separate planes which are oblique to the frontal and sagittal planes. In a similar manner, orthogonal Lead 8 may serve as a polar lead in place of Lead 13. In this case Leads 1, 2, 3, and 8, together with their reciprocals, and also Leads 9, 10, 11, and 8, together with their reciprocals, each lie on separate additional planes which are oblique to the transverse and frontal planes. Finally, orthogonal Lead 6 also may be considered to be a polar lead; then Leads 1, 6, 3, and 4, together with their reciprocals, and, in like manner, Leads 9, 6, 11, and 12, together with their reciprocals, each lie on separate additional planes which are oblique to the sagittal and transverse planes. No formal attempt will be made at this time to give the angular

TABLE I

LEAD NUMBER	AZIMUTH (ϕ)	ALTITUDE (θ)	LEAD DESIGNATION	LEAD VOLTAGE	EQUALIZING FACTOR
1	135°	−35°	$\frac{-X-Y+Z}{3}$	$\frac{(E_x'+E_y'+E_z)-(E_x+E_y+E_z')}{3}$	1.73 or $\sqrt{3}$
2	90°	−45°	$\frac{-Y+Z}{2}$	$\frac{(E_y'+E_z)-(E_y+E_z')}{2}$	1.41 or $\sqrt{2}$
3	45°	−35°	$\frac{+X-Y+Z}{3}$	$\frac{(E_x+E_y'+E_z)-(E_x'+E_y+E_z')}{3}$	1.73 or $\sqrt{3}$
4	0°	−45°	$\frac{+X-Y}{2}$	$\frac{(E_x+E_y')-(E_x'+E_y)}{2}$	1.41 or $\sqrt{2}$
5	135°	0°	$\frac{-X+Z}{2}$	$\frac{(E_x'+E_z)-(E_x+E_z')}{2}$	1.41 or $\sqrt{2}$
6	90°	0°	$+Z$	(E_z-E_z')	1.00
7	45°	0°	$\frac{+X+Z}{2}$	$\frac{(E_x+E_z)-(E_x'+E_z')}{2}$	1.41 or $\sqrt{2}$
8	0°	0°	$+X$	(E_x-E_x')	1.00
9	135°	35°	$\frac{-X+Y+Z}{3}$	$\frac{(E_x'+E_y+E_z)-(E_x+E_y'+E_z')}{3}$	1.73 or $\sqrt{3}$
10	90°	45°	$\frac{+Y+Z}{2}$	$\frac{(E_y+E_z)-(E_y'+E_z')}{2}$	1.41 or $\sqrt{2}$
11	45°	35°	$\frac{+X+Y+Z}{3}$	$\frac{(E_x+E_y+E_z)-(E_x'+E_y'+E_z')}{3}$	1.73 or $\sqrt{3}$
12	0°	45°	$\frac{+X+Y}{2}$	$\frac{(E_x+E_y)-(E_x'+E_y')}{2}$	1.41 or $\sqrt{2}$
13	—	90°	$+Y$	(E_y-E_y')	1.00

locations of the various leads on these 6 "oblique" planes, since such planes have not yet been defined in vectorcardiographic notation.[9,10] However, the general arrangement of the lead axes in these 6 "oblique" planes is depicted in Fig. 3,*B*.

The angular location of the mean P, QRS, and T vector projections on each of the 9 planes can be determined by estimating the angular location of the transitional P, QRS, and T patterns on the plane in question. The direction of inscription of the projection of the QRS loop on each of these 9 planes may be estimated usually by noting the configuration, i.e., RS or QR, which the transitional QRS complex takes on any given plane, and the general contour of the projection of the QRS loop can be ascertained. From the projections on each of the several planes the approximate configuration of the spatial QRS loop and the mean spatial P and T vectors can be visualized.

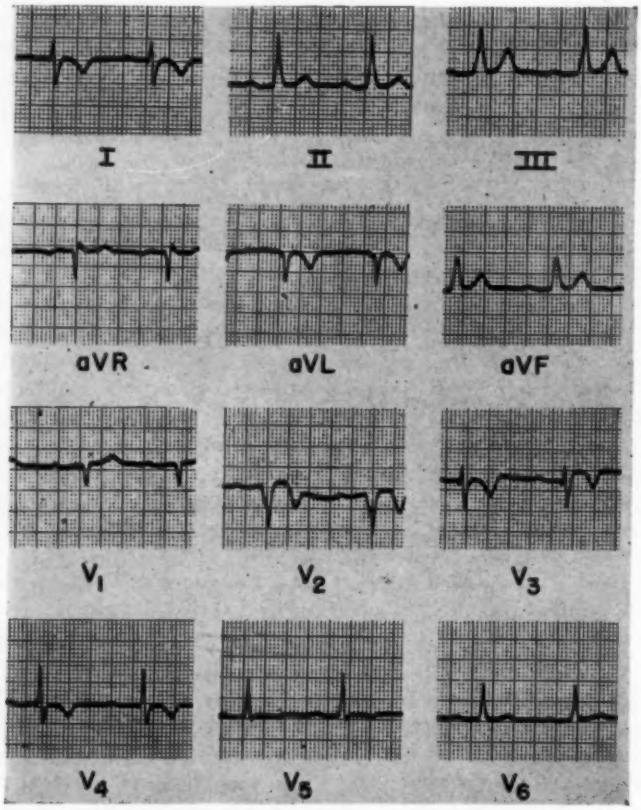

Fig. 1.—Twelve lead clinical electrocardiogram of a patient with an anterior myocardial infarction and first degree auriculoventricular block.

In addition to the presentation of these 9 well-defined planes which aid in the synthesis of the scalar tracings into spatial vector electromotive forces, the arrangement of leads shown in Fig. 2 is analogous to the spatial mosaic formed by multiple "unipolar" thoracic leads,[11,12] without the distortion of the latter which results from both proximity of the unipolar electrode in the precordial region and deviation of the thorax from a cylindrical contour. A null pathway[11,12] always can be traced when the 13 leads (and their reciprocals) are arranged in the manner illustrated in Fig. 2. Thus, the locations of various areas, such as those containing mean positive deflections, mean negative deflections, Q waves of significant duration,[13] etc., may be mapped spatially.

The 13 scalar leads may be recorded rapidly by means of a specially constructed switching box, the dial panel of which is illustrated in Fig. 4. The left and right arm wires of the electrocardiograph are connected to the + and − terminals, respectively, of the switching box. The

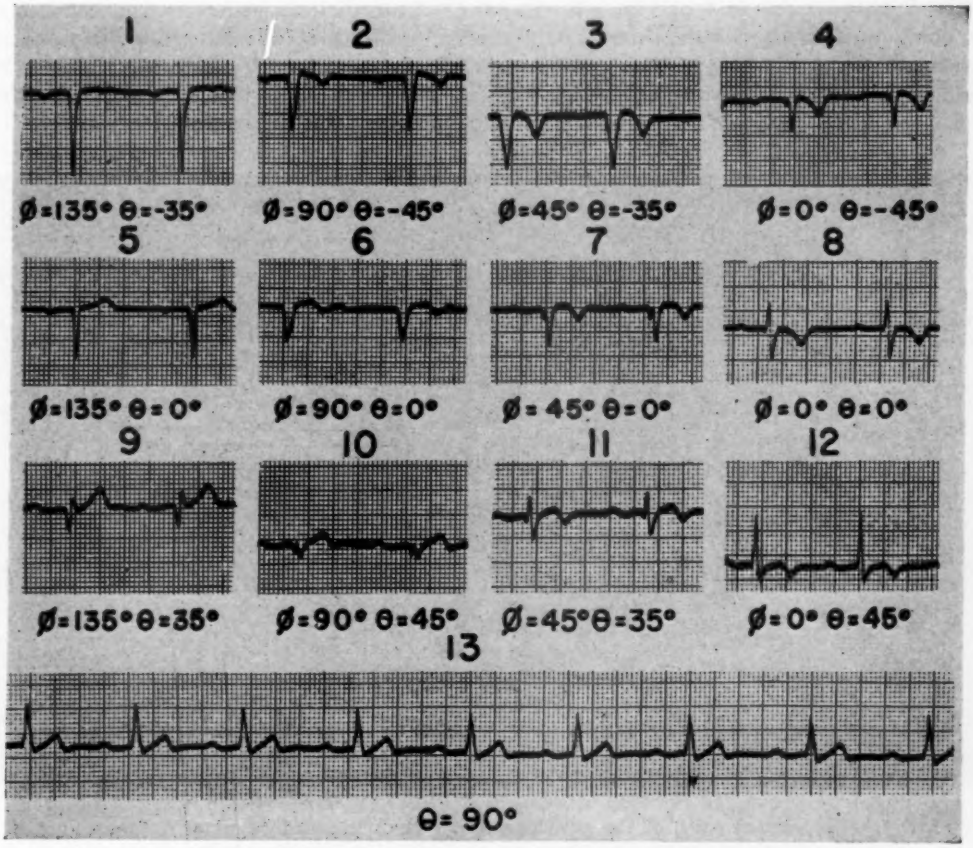

Fig. 2.—Thirteen lead electrocardiogram recorded in the manner described in the text. (Same patient as in Fig. 1.)

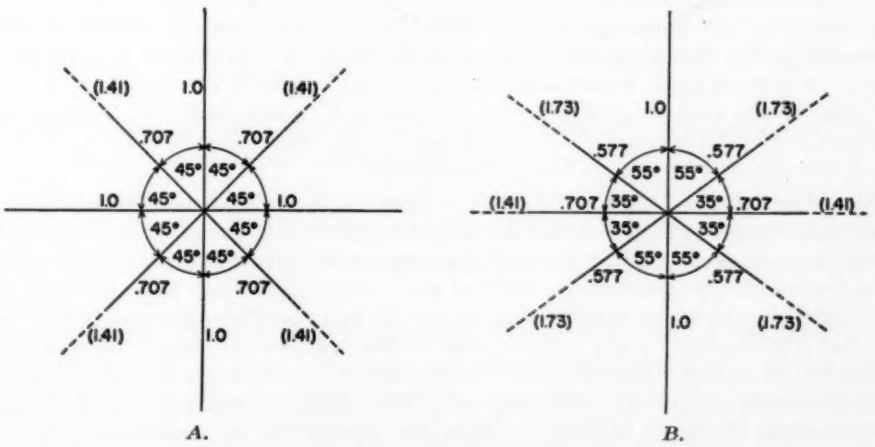

Fig. 3.—*A*, The arrangement of the lead axes on the frontal, sagittal, and transverse planes. *B*, The arrangement of the lead axes on the 6 "oblique" planes described in the text. In both *A* and *B* the solid lines represent the "normal" magnitudes of the lead axes. The lead magnitudes multiplied by their respective equalizing factors (in parentheses) yield leads of equal magnitudes (solid and dotted lines).

+X, +Y, and +Z terminals and the −X, −Y, and −Z terminals of the box are connected to the patient in accordance with the description of the vectorcardiographic reference frame previously published.[3] The switching box is adequately grounded by means of the ground terminals. When Leads 6, 8, and 13 (left-hand dial) are recorded, the lower right dial is set at 1. When Leads 2, 4, 5, 7, 10, and 12 (middle dial) are taken, the lower right dial is placed on $\sqrt{2}$. Finally, when

Fig. 4.—The control panel of the switching box. The unmarked terminals represent grounding posts. The connections to the marked terminals, as well as the function and operation of the 5 dials, are described in the text. The protrusions on the left side represent the adjustment screws of the variable resistors described in the text.

Leads 1, 3, 9, and 11 (right-hand dial) are recorded, the lower right dial is set at $\sqrt{3}$. When the lower left dial is set at "normal," the leads are recorded with their normal magnitude. In such an instance, the equalizing factors listed in Table I may be introduced by adjusting the gain control dial of the electrocardiograph. Thus, for Leads 6, 8, and 13, the electrocardiograph is adjusted to yield a deflection of 1 cm. per 1 mv. of input. For Leads 2, 4, 5, 7, 10, and 12 this deflection, for 1 mv. of input, is increased to 1.41 cm.; and, for Leads 1, 3, 9, and 11, it is increased to 1.73 cm. These equalizing factors may be introduced automatically by adjusting the electrocardiograph to yield a deflection of 1.73 cm. per 1 mv. of input for all 13 leads and by setting the lower left dial of the switching box at "equalized."

The wiring diagram of the switching box is shown in Fig. 5. The value of R for the resistors may be any convenient value, provided that, without introducing alternating current interference, it is sufficiently large to abolish effectively the errors which would otherwise result from differences of the resistances between the skin and the various electrodes. Common mode rejection of alternating current interference is obtained by the fact that the resistances in the two limbs of any lead are balanced. From measurement of electrode-skin resistance of the various electrodes used in the author's reference frame[3] by the method of Gentile,[14] an R value of 50,000 ohms seems to be satisfactory, as this effectively eliminates significant deviations from the calculated angular locations of the 13 lead axes. Since the introduction of accurate equalizing factors through the placement of the lower left dial at "equalized" depends on a rather critical constancy of the resistances in the positive and negative limbs of any given lead from patient to patient, additional resistors of 3R have been introduced into this particular portion of the circuit. For equalization of the lead magnitudes the shunt resistance for Leads 5, 8, and 13 of the left-hand

dial (S_1 of Fig. 5) was calculated to be 10.9R; and the shunt resistance for Leads 2, 4, 5, 7, 10, and 12 of the middle dial (S_2 of Fig. 5) was calculated to be 31.1R. Such resistances were introduced into the circuit in the form of variable resistors which were adjusted by trial and error to yield the desired attenuation of these leads in a group of patients. The variable resistors then were locked in their experimentally determined positions.

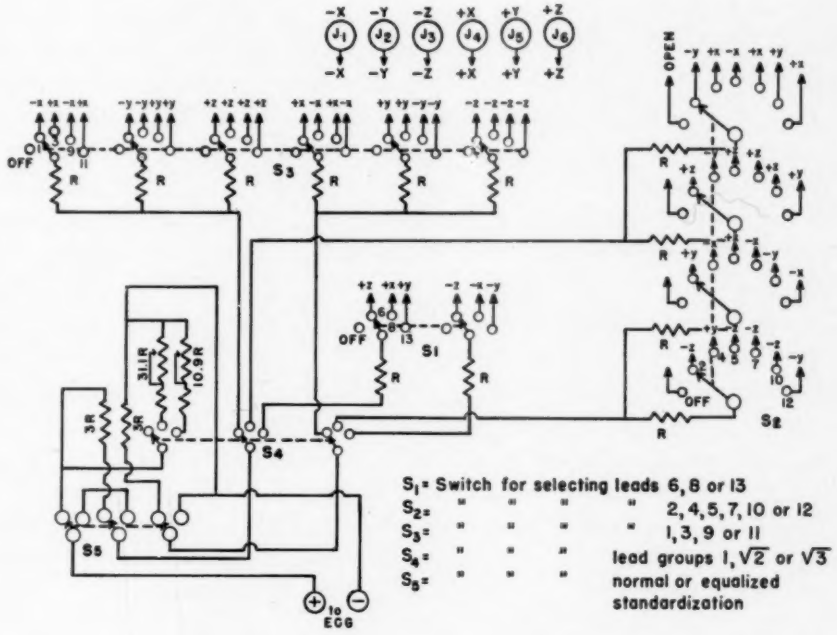

Fig. 5.—Wiring diagram of the switching box. A satisfactory value for R is 50,000 ohms. All resistors are wire-wound. See text.

DISCUSSION

The switching box described and illustrated herein has been designed for a reference frame formed by orthogonal leads of equal magnitudes. If leads of unequal magnitudes are to be used,[1,2,15] the circuit must be modified or the leads must be equalized by cathode followers[2] before introduction into the switching box.

When compared with cathode-ray vectorcardiographic loops, the 13 lead scalar presentation has several practical advantages:

1. The only equipment necessary is the usual single-channel electrocardiograph, which may be of the direct-writing type, and the small portable switching box. (The circuit of the latter could be incorporated into the electrocardiograph.)

2. Since the method of presentation is scalar, it can be grasped readily by those trained in clinical electrocardiography, whereas cathode-ray vectorcardiographic presentation necessitates a frequently difficult reorientation of the thought processes of the experienced electrocardiographer. (Nevertheless, the grouping of the 13 interrelated scalar tracings is such that interpretation by vector methods is much simpler than in the case of the present-day clinical electrocardiogram in which 12 leads are recorded in a rather haphazard manner.)

3. The configurations displayed by the various combinations of the 3 orthogonal leads depend not only upon the scalar contours of the latter but also upon the relationships between the simultaneously occurring electrical events which they record. If, for example, the orthogonal leads consisted of *identical* monophasic upward deflections, their combinations might display a wide variety of different contours, depending upon the phase relations of the deflections in the 3 orthogonal leads. Planar vectorcardiography shows the phase relationships between only 2 of the orthogonal leads recorded simultaneously.

4. In addition to QRS configurations, this system of display permits the accurate visualization of P, ST, T, and U data, as well as the measurement of time intervals between deflections and the delineation of arrhythmias, all of which are difficult or impossible when the same data are presented in the form of planar or stereoscopic vectorcardiograms on stationary time scales.

Except for the ease and rapidity of recording and the more rational arrangement of leads in space, the possible advantages of the 13 leads, recorded in the manner described, over the 12 leads of the routine clinical electrocardiogram are problematic at the present time. Indeed, the ultimate value of the 13 lead presentation will depend in large measure upon how it compares with multiple precordial leads in the diagnosis of localized myocardial lesions. There is no doubt that a myocardial infarction of sufficient size or of such location as to produce marked changes in the usual precordial V leads will produce similar diagnostic changes in the 13 lead tracing, as is clearly evident from a comparison of Figs. 1 and 2. However, whether changes which are more subtle, but which electrocardiographers have found from experience to be significant, such as diminution in the size of an R wave in precordial V leads taken from right to left across the chest, will always be apparent in the 13 lead system is theoretically debatable and must be decided practically by comparative studies in patients. Such a project is being pursued in this laboratory, and, at the present time, no cases of myocardial infarction diagnosed by multiple precordial leads have failed to reveal diagnostic abnormalities in the 13 lead tracing. This is in accord with the earlier findings of Milnor and his associates,[8] and with the more recent statement of Newman[16] and associates: "Between the observations of Milnor and ourselves, we have examined over a thousand subjects with all sorts of abnormalities. We have yet to find information which is of any use for clinical correlation or interpretation in the electrocardiograms obtained from multiple surface leads which cannot be derived from three simple bipolar electrocardiographic leads taken at a distance, representing the electrical information in the three axes of the body." It should be emphasized, however, that such information is not forthcoming if the 3 leads are obtained separately, rather than recorded either simultaneously with a multi-channel electrocardiograph or in various combinations, such as those suggested in this communication, with a single-channel electrocardiograph. Fig. 2 fails to reveal QRS abnormalities absolutely diagnostic of a myocardial infarction in any of the 3 orthogonal leads (Leads 6, 8, and 13), since a QS pattern sometimes can be obtained normally in Lead 6, representing the sagittal lead, just as a QS may be found normally in V_1 and V_2 and even occasionally in V_3.

It is quite likely that the 13 lead presentation of 3 orthogonal leads will greatly simplify the voltage criteria now in common use for the diagnosis of left and right ventricular hypertrophy.[17-19] In place of setting up multiple criteria based upon the QRS voltage in various single leads or combinations of leads, it would seem entirely possible that a certain minimum voltage for the largest QRS deflection in any of the 13 equalized leads would serve to indicate the presence of hypertrophy.

The presentation of orthogonal leads by means of a group of 13 leads is convenient and feasible, but its ultimate place in clinical cardiology is conjectural. At the present time it is suggested as an interesting research tool for comparison both with the stereoscopic vectorcardiogram obtained with the same reference frame[20] and with the 12 lead clinical electrocardiogram.

SUMMARY

A method of presenting the information obtainable in 3 orthogonal leads by means of a display of 13 leads representing the single, double, and triple combinations of the former has been described. Such a display represents the rational arrangement of certain selected scalar derivatives of the spatial vectorcardiogram, and facilitates the interpretation of the electrical data collected from the body surface in terms of vector principles. The details of the construction and operation of a switching box* for the rapid recording of these 13 scalar leads have also been given.

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*The switching box described herein was designed and constructed in accordance with the author's specifications by Engineering Specialties, 7706 Shawnee Run Road, Madeira, Ohio.

QUANTITATIVE BALLISTOCARDIOGRAPHY IN AORTIC INSUFFICIENCY

With a Note on the Hemodynamic Effects of a Hufnagel Valve

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INTRODUCTION

THE heaviest left ventricles are associated with aortic insufficiency,[1] although the pressure-volume component of cardiac work in this condition is said to be normal or but moderately increased.[2,3] Ventricular hypertrophy is related rather to the work of imparting momentum to the blood. The ultra-low-frequency ballistocardiograph measures the impulse of force equivalent to body momentum change, and is, therefore, ideally suited to the study of aortic insufficiency. With recording systems which largely eliminate body distortion the ballistic deflections may be related to discrete physiologic events and force expressed in absolute units.[4,5] In this investigation, an "aperiodic" ballistocardiograph is employed to measure the hyperkinesis of aortic insufficiency, to estimate the magnitude of cardiac kinetic work as reflected by body motion, and to study the hemodynamic effects of a Hufnagel valve.

Though the origin of the systolic ballistic waves is known,[4] the diastolic complex is less well understood. Because the aortic standing wave is diminished or absent in advanced aortic insufficiency,[6] the ballistocardiograms of such patients may be utilized to elucidate the role of the standing wave in the genesis of diastolic vibrations.

METHODS

All records were made with the modified Wittern ballistocardiograph, previously described.[5] The apparatus consisted of a 10.5 pound aluminum frame suspended with aperiodic damping, 2 degrees of freedom, and a natural frequency of 0.3 c.p.s. Acceleration in and 90 degrees to the long axis of the platform was measured directly in the range 0.5 to 25 c.p.s. Calibration force was provided by a motor-driven pendulum fixed to the platform; displacement was measured mechanically in millimeters after removing the frictional damper. After a 10-minute rest, frontal plane force was recorded over several complete respiratory cycles at paper speed 50 mm. per second. In some subjects, force

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was also measured in the sagittal plane by positioning the subject on his right side. Longitudinal and lateral systolic amplitude were averaged over one complete respiratory cycle and expressed as frontal plane ejection force, using the convention and normal standards previously reported.[5]

RESULTS AND DISCUSSION

1. *Relationship Between Force and Degree of Insufficiency.*—With clinically significant regurgitation, stroke force ranged between 150 and 550 per cent of maximum normal. The parallelism between ballistic amplitude and the degree of insufficiency is demonstrated in Table I. Only congestive failure and aortic aneurysm modified this relationship.

a. *Influence of congestive failure:* Stroke volume and stroke acceleration, the chief determinants of systolic ballistic amplitude,[4] are decreased by myocardial insufficiency.[7] It is therefore not surprising that Patient 2, who was in severe failure, had quantitatively normal reaction force despite a Grade 3 aortic diastolic murmur, wide pulse pressure, and capillary pulsation. The records of 2 comparable patients were too disordered to quantitate. In contrast, hyperkinesis was present in 8 patients previously in failure but examined after full compensation had been restored. All 5 patients with force greater than 250 per cent of maximum normal are included in this group, suggesting that a critical level of kinetic work exists, beyond which circulatory failure is likely to follow.

b. *Effect of aortic aneurysm:* Patient 5 had syphilitic heart disease with an ascending arch aneurysm, left ventricular enlargement, Grade 4 aortic diastolic murmur, and classical peripheral signs; but despite full cardiac compensation, her reaction force was only 19.2×10^5 dynes, 155 per cent of maximum normal. In a hydraulic system with a relatively constant volumetric rate of flow, acceleration is limited by linear velocity, which in turn is inversely proportional to cross-sectional area of the conduit. Because of the aneurysm in Patient 5, acceleration of the stroke volume and ballistic system must have been considerably less than in Patients 10 and 12, who had comparable syphilitic heart disease without aneurysm, and with a reaction force 246 and 316 per cent maximum normal.

2. *Effect of Co-Existing Valvular Lesions.*—Patient 1 had a Grade 4 rasping basal systolic murmur transmitted to the apex and neck, associated with a coarse thrill, absent second sound, and marked left ventricular enlargement. He also had a Grade 2 aortic diastolic murmur, no peripheral signs of aortic insufficiency, and normal reaction force. The systolic ventriculoaortic pressure gradient was 88 mm. Hg, and at necropsy the aortic valve was replaced by a thick immovable diaphragm with an irregular orifice approximately 5 mm. in diameter. The mitral valve was normal.

Patient 3 was never in failure, but in addition to mitral stenosis and insufficiency had a Grade 2 basal diastolic murmur without peripheral signs of aortic insufficiency. His reaction force was at the upper limit of normal. Patient 4 was similar except for the presence of capillary pulsation, and force slightly in excess of normal. Patients 7 and 8, on the other hand, had aortic diastolic murmurs, left ventricular enlargement, prominent neck pulsation, Corrigan

TABLE I. RELATIONSHIP BETWEEN FORCE AND CLINICAL FINDINGS IN 13 PATIENTS WITH AORTIC INSUFFICIENCY

PATIENT	AGE	SEX	ETIOLOGY AND A.H.A. CLASSIFICATION	LESION*	LT. VENTRICULAR ENLARGEMENT	ECG	DIGITALIS	BRACHIAL BLOOD PRESSURE	AORTIC DIASTOLIC MURMUR INTENSITY 1 TO 4+	AORTIC SECOND SOUND	PERIPHERAL SIGNS 0 TO 4+	FORCE/STROKE DYNES × 10^5/S.M.B.S.A.	PER CENT MAXIMUM NORMAL	FORCE/MINUTE DYNES × 10^6/S.M.B.S.A.	PER CENT MAXIMUM NORMAL
1.	32	M	RHD 2C	AS ai	+	LVH	+	102/84	2+	+	0	10.1	0	8.1	0
2.	77	M	RHD ASHD 4D	AI angina failure	+	LBBB	+	240/0	3+	0	3+	10.2	0	7.6	0
3.	22	M	RHD 1A	MS MI ai	0	Normal	0	118/58/36	2+	+	0	12.2	0	7.6	0
4.	25	M	RHD 2B	AI MS MI	0	LAD	+	142/58	2+	+	1+	16.9	138	11.6	123
5.	50	F	SHD 2C	AI aneurysm	+	LVH	+	188/0	4+	0	4+	19.2	155	15.8	167
6.	50	M	SHD ASHD 2C	AI	+	? LVH	+	182/40	3+	+	2+	20.2	162	17.3	183
7.	48	M	ASHD 2B	AI ? ruptured cusp	+	? LVH	+	128/68	4+	+	1+	20.7	167	18.9	199
8.	62	M	RHD 3C	AI ms mi	+	LVH	+	140/56	2+	+	2+	23.0	186	15.4	162
9.	22	M	RHD 2B	AI ms mi	+	LVH	0	146/20	3+	+	3+	28.9	233	25.8	274
10.	50	M	SHD 3C	AI angina	+	LVH PMI	+	152/20	3+	0	3+	33.2	268	23.6	246
11.	34	F	RHD 3D	AI	+	LVH	+	182/0	4+	+	4+	35.5	286	25.8	275
12.	73	M	SHD 3C	AI	+	LVH	+	188/22/0	4+	0	4+	39.2	316	35.8	376
13.	31	M	CHD 3D	AI coarctation angina	+	LVH	+	330/120/0	4+	0	4+	47.5	384	42.0	442

Abbreviations: RHD, SHD, CHD, and ASHD indicate, respectively, rheumatic, syphilitic, congenital, and arteriosclerotic heart disease. AI (ai), AS, MI (mi), and MS (ms) indicate aortic insufficiency, aortic stenosis, mitral insufficiency, and mitral stenosis. LAD, LVH, LBBB, and PMI indicate left axis deviation, left ventricular hypertrophy, left bundle branch block, and posterior myocardial infarction. "Force" indicates sum of headward and right-left ejection forces. A.H.A. is the American Heart Association. S.M.B.S.A. denotes square meter body surface area.

*Predominant lesion capitalized.

pulse, and capillary pulsations despite significant coexisting mitral disease. Reaction force was markedly increased in both.

In each patient with combined valve lesions, ballistic amplitude varied with the dynamic importance of aortic insufficiency. One of the most common and difficult problems in selecting patients for cardiac surgery is that posed by the basal diastolic murmur, and in an attempt to meet the need for quantitative criteria, the difficult and somewhat hazardous technique of left heart catheterization has been developed.[8] The above data suggest that with experience the degree of aortic insufficiency beyond which surgery would be unwise might be determined ballistocardiographically with accuracy and safety.

3. *Effect of a Thoracic Aortic Valve.*—The relationship between the degree of insufficiency and ballistic force is best illustrated by a measured change in a single individual. In this way clinical estimates of severity are avoided, and, since force is constant in a given individual,[5] the conditions of a controlled experiment are approximated. Because Patient 14 illustrates such a change, as well as complications secondary to a new operative technique, his case is presented in detail.

In 1942, at age 11 years, M. C. had the first of many attacks of acute rheumatic fever, and in June 1954, was admitted to the Strong Memorial Hospital with congestive failure and acute carditis. Cortisone was ineffectual, but with rest, digitalis, and salicylates he gradually recovered, and in September 1954, was admitted for cardiac surgery, presumably free of rheumatic activity.

He was a slight, young adult whose extreme pulsations moved his ear lobes and head, distended the neck and thoracic inlet, and forcefully lifted the entire anterior chest wall. His temperature was 37.8° C.; pulse 98; blood pressure, left arm 186/0 mm. Hg, left leg 270/0 mm. Hg. The heart was enlarged to the sixth intercostal space and midaxillary line. The first sound was normal; the aortic second sound was of low intensity, and a loud mid-diastolic gallop was both audible and visible. Short Grade 2 mitral systolic and mid-diastolic murmurs were heard, and at the base a short systolic murmur was followed by a Grade 4 decrescendo diastolic murmur which was widely transmitted. The radial pulse exhibited both water-hammer and collapsing qualities; and Duroziez's sign, capillary pulsations, and retinal arterial "blinking" were demonstrable. Throat cultures were negative, and the titer of antistreptolysin O had fallen from 2,000 on June 18, 1954, to 250 units per c.c. He had left ventricular hypertrophy by ECG and x-ray, but no evidence of mitral disease.

Under cyclopropane-ether anesthesia, an 8 cm. segment of aorta was freed just distal to the left subclavian artery, and a Hufnagel valve inserted. Postoperatively, pressure in the arms ranged between 180 and 240/0 mm. Hg, in the legs between 190/100 and 260/108 mm. Hg; capillary pulsation disappeared from the toes. Head-nodding increased, and over the upper third of the body, superficial vessels previously unnoticed pulsated vigorously. Even retinal veins "blinked" in systole, and the patient complained of throbbing headache. The aortic diastolic murmur was at least as long and loud as prior to operation. From the surgical standpoint however his postoperative course was benign, and he was discharged Nov. 19, 1954.

On Feb. 3, 1955, he was admitted to the Penn Yan Hospital in shock, with flank pain, vomiting, and hematuria. Though he recovered spontaneously, sudden numbness of the left foot prompted readmission to the Strong Memorial Hospital on Feb. 15, 1955. Physical findings were unchanged except for decreased loudness and pitch of clicking of the valve, loss of the diastolic gallop, and an absent dorsalis pedis pulse. An intravenous pyelogram revealed a virtually nonfunctioning right kidney; retrogrades were normal. Numerous blood cultures, treated technically for possible subacute bacterial endocarditis, were negative. Paroxysms of substernal pain unrelieved by nitroglycerin, as well as the first of many attacks of supraventricular tachycardia, complicated the course. Though he was discharged on maintenance Tromexan, he sustained an embolus to the right femoral artery on April 9, 1955; embolectomy was performed successfully 8 hours later.

During a brief hospitalization for Dicumarol toxicity in September, 1955, return of renal function and marked decrease in heart size were demonstrated. The diastolic murmur was definitely shorter and less intense, and pulsations were markedly diminished. He was free of dyspnea, no longer required digitalis or salt restriction, and except for occasional precordial pain was unquestionably improved. On Dec. 2, 1955, however, he sustained a second femoral artery embolus, and again embolectomy was successful. On Dec. 10, 1955, severe, constant, nonradiating substernal pain began, was unrelieved by nitroglycerin, and was unassociated with hypotension, dyspnea, or electrocardiographic change. Over the following 24 hours pain increased in intensity, became decidedly throbbing in character and extended into the neck. Blood pressure remained stable despite a fall in hematocrit, and on Dec. 25, 1955, he expired during a sudden exacerbation of pain. The valve site was thought by most observers to be the site of origin of both emboli and dissecting aneurysm, but post-mortem confirmation was not permitted.

TABLE II. EFFECT OF A HUFNAGEL VALVE ON THE SYSTOLIC BALLISTIC FORCE OF PATIENT 14

DATE	FORCE/STROKE DYNES × 10^5/ S.M.B.S.A.	PER CENT MAXIMUM NORMAL	FORCE/MINUTE DYNES × 10^6/ S.M.B.S.A.	PER CENT MAXIMUM NORMAL
Preoperative				
Nov. 1, 1954	67.9	548	48.7	513
Postoperative				
Nov. 13, 1954	75.1	606	62.5	656
Feb. 26, 1955	71.2	576	55.4	584
April 4, 1955	63.6	514	49.1	517
July 7, 1955	55.7	449	40.4	425
Nov. 30, 1955	51.3	414	38.6	407

Change in reaction force in the year following surgery is presented in Table II. Note that the early postoperative period was associated with a significant increase in force. Wiggers[7] emphasized that the regurgitant volume depends in part upon the aorticoventricular pressure gradient, which varies with stroke volume, arterial compliance, and peripheral resistance. Hasenfeld and Romberg[9] demonstrated a decrease in vasoconstrictor tone in dogs and rabbits with experimental aortic insufficiency, and the importance of vasodilatation in facilitating runoff was emphasized by Stewart[10] and Hewlett and Van Zwaluwenburg.[11] Gorlin[2] and his colleagues noticed that the warm, moist, flushed skin and the capillary pulsation so characteristic of aortic insufficiency are confined to the upper half of the body in patients with Hufnagel valves, and suggested that vasodilatation depends upon local vascular reflexes. Postoperatively, Patient 14 exhibited diastolic hypertension without capillary pulsation in the lower half of the body, a reaction which might have been anticipated if, preoperatively, vasomotor tone had been tonically suppressed. Outflow from the proximal aorta cannot begin until diastolic pressure, set by distal segment vasomotor tone, is exceeded. It is therefore probable that vasoconstriction, together with the impedance of the valve itself, initially delayed and decreased the rate of runoff, as well as the retrograde flow. This would shift the proximal "windkessel" to a higher systolic point on its pressure-volume diagram, and cause it to "store" under high pressure an additional volume capable of promptly regurgitating into the ventricle. The rise in brachial artery systolic pressure, lack of decrease in murmur intensity, and increased extracirculatory motion suggest that the volume regurgitated from the proximal vessels was comparable to the retrograde

flow prevented by the valve. With time, however, adaptive changes in vascular tone distal to the prosthesis, in arterial compliance proximal to it, and perhaps also in ventricular function, would result in an increasingly large net decrease in regurgitant volume, ballistic amplitude, and heart size. The above formulation suggests that vasodilator drugs might be used with profit to ease the stress of the early postoperative period.

4. *Estimation of Kinetic Work Expenditure in Aortic Insufficiency.*—The striking pulsatile movements of Patient 14 motivated us to estimate ballistocardiographically the order of magnitude of kinetic work increase in severe aortic insufficiency. To this end the sum of longitudinal and lateral forces and of longitudinal and lateral displacements are compared for Patient M. C. and a normal young adult:

Normal Subject:	longitudinal force	6.3×10^5 dynes
	lateral	3.4×10^5 dynes
	sum	9.7×10^5 dynes
	longitudinal displacement	0.011 millimeters
	lateral	0.003 millimeters
	sum	0.014 millimeters
Patient 14 (at rest):	longitudinal force	35.6×10^5 dynes
	lateral	32.3×10^5 dynes
	sum	67.9×10^5 dynes
	longitudinal displacement	0.12 millimeters
	lateral	0.06 millimeters
	sum	0.18 millimeters

After mild exercise (5 sit-ups) M. C.'s force more than doubled, but displacement could not be measured because of respiratory artifact.

The total work of a normal resting heart is on the order of 5 kilogram meters per minute, of which but 0.05 to 0.25 kilogram meters are expended in imparting momentum to the blood.[12] Since there is no appreciable difference in force direction, the normal ballistocardiogram and that of aortic insufficiency probably represent comparable fractions of cardiac kinetic energy expenditure. Assuming peak ballistic force and displacement to be simultaneous and in the same direction, their product denotes the maximum kinetic work measureable as body motion. M. C.'s systolic force was 7 times normal, displacement 13 times; their product should therefore be 91 times the normal range of 0.05 to 0.25 kilogram meters, or between 4.5 and 22.5 kilogram meters. The reason for the extreme ventricular hypertrophy is apparent, for M. C.'s kinetic work probably exceeds the total work of a resting normal heart. Pressure-volume work and regurgitant volume are markedly increased by vasoconstriction, exercise, and tachycardia. Since the kinetic factor, $\left[\frac{MV^2}{2g}\right]$ varies as the cube of the total cardiac output, stresses

which normally effect negligible increases in load impose enormous demands upon the heart handicapped by aortic insufficiency.

As a corollary to the above figures, systolic reaction forces related to flow are, in the absence of hyperkinesis, originated by a small fragment of cardiac energy expenditure, and do not reflect cardiac "strength" or "weakness." It is rather the hyperkinetic states (aortic insufficiency, arteriovenous fistulae, beriberi, hyperthyroidism, pheochromocytoma, and congenital shunts) for which the ballistic technique is theoretically best suited.

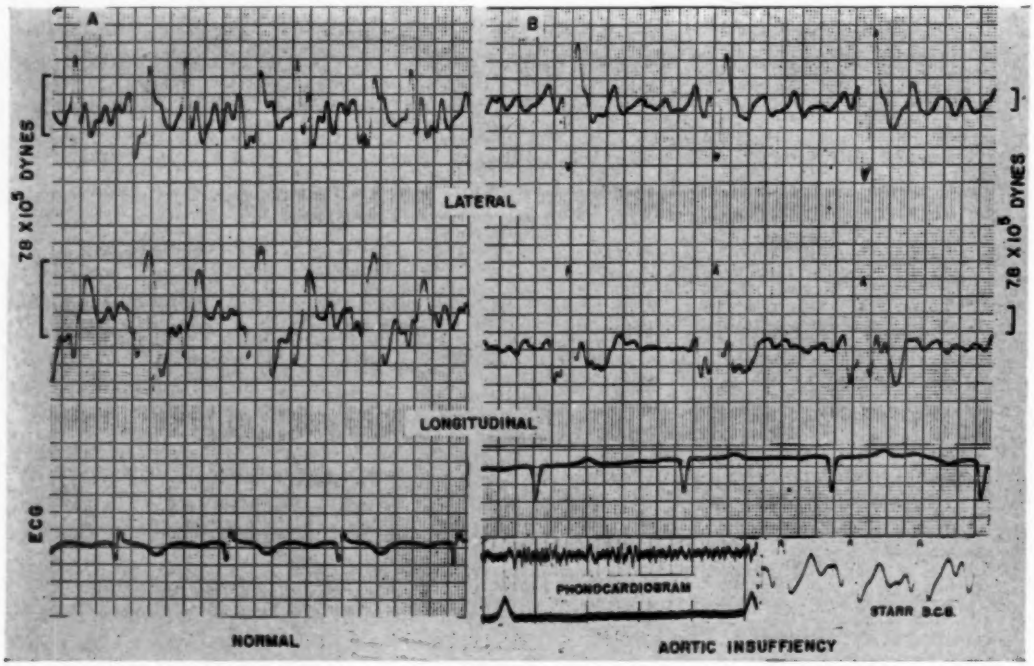

Fig. 1.—Normal ballistic wave form is contrasted with that of severe aortic insufficiency. A phonocardiogram and high-frequency ballistocardiogram are provided for reference. Note particularly the calibration difference, absence of the second sound, and virtual absence of diastolic waves in the "aperiodic" record. In contrast, aftervibrations produce normal-appearing diastolic waves in the high-frequency tracing.

5. *The Diastolic Ballistic Complex and the Aortic Standing Wave.—A* and *B* of Fig. 1. contrast normal wave morphology with that characteristic of severe aortic insufficiency (Patient 10). Representative beats from a Starr high-frequency bed, as well as a stethoscopic phonocardiogram recorded at Erb's point are provided for reference. Note particularly the absence of the aortic second sound, and the virtual absence of diastolic waves in the ultra-low-frequency ballistocardiogram. Wiggers[13] and Alexander[6] showed that the dicrotic wave in central pressure pulses depends upon the aortic standing wave, and that in aortic insufficiency the dicrotic wave diminishes and descends. Although the pulse wave is reflected from the periphery in experimental total aortic insufficiency, the standing wave is abolished, presumably because the central end of the aortic "resonator" is open.[6] The authors produced large ballistic deflections with mass motions originated by a standing wave in a closed elastic tube,[4] and obtained similar results with aortic injection experiments in dogs.[14] Patient

10 had no aortic second sound, nor did Patients 5 and 13 with morphologically similar records. The second sound was present but diminished in Patients 11 and 14, both of whom had abnormally small diastolic ballistic waves. Patients 4, 6, 7, 8, and 9, however, had normal second sounds and diastolic complexes. It seems probable, therefore, that virtually complete absence of aortic valve function is necessary before arterial resonance and the diastolic ballistic waves are altered.

Fig. 1,*B* also demonstrates the importance of eliminating body distortion in clinical ballistocardiography. Aftervibrations originated by systolic forces produced normal-appearing diastolic ballistic waves in the Starr record despite the absence of cardiovascular forces.

SUMMARY AND CONCLUSIONS

1. In 14 unselected patients with aortic insufficiency, including 5 with combined valve lesions, systolic reaction force varied directly with the degree of insufficiency as judged clinically, unless congestive failure or aortic aneurysm coexisted. The data suggest the usefulness of quantitative force ballistocardiography in safely selecting patients for cardiac surgery.

2. A detailed case report of a patient in whom a Hufnagel valve was inserted is presented. Though post-mortem data are unavailable, it is probable that embolization and aortic dissection originated from the site of the prosthesis.

After insertion of the Hufnagel valve a striking transient increase in systolic force was followed by a steady decrease and relief of the symptoms of cardiac insufficiency. Hemodynamic factors responsible for these changes are discussed.

3. Cardiac kinetic work in severe aortic insufficiency was estimated ballistocardiographically and found to equal or exceed the total work of a resting normal heart.

4. In patients with free aortic regurgitation, arterial diastolic resonance is lost or diminished, together with the chief ballistic diastolic vibrations. It is probable, therefore, that mass motions originated by the standing wave are partly responsible for the normal ballistic diastolic complex.

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THE INTERRELATIONSHIP BETWEEN COR PULMONALE, CAPILLARY BED RESTRICTION AND DIFFUSION INSUFFICIENCY FOR OXYGEN IN THE LUNG

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THE era of "organ physiology" is rapidly fading. Single organs no longer can be adequately studied as if they existed within a vacuum, unaffected by changes taking place elsewhere in the body. Recognition of this basic precept has paved the way for a number of recent advances in our understanding of cardiac disorders—advances which would have been impossible had not simultaneous measurements been made of various organ functions.

Application of these broader study techniques has made especially clear the integral relationship which exists between cardiac and pulmonary function. That alterations in alveolar ventilation may affect circulatory dynamics within the pulmonary vascular bed has been suggested for sometime,[1] but many aspects of this active physiologic partnership remain poorly defined. The present report is designed to bring into sharper focus certain facets of cardiopulmonary study which may prove useful in the evaluation of several groups of cardiac patients.

One of the best-known examples of the ventilatory-circulatory relationship is that which exists in those situations that are linked together by the common denominator of increased pulmonary "arteriolar" resistance. Such increases in resistance may be divided into two categories with respect to etiology—those which are "functional" and reversible; and those which are "organic" and irreversible. The "functional" form is a consequence of alveolar hypoventilation[2,3,4] such as may be produced by abnormalities operating in states such as emphysema, bronchial asthma, kyphoscoliosis,[5,6] and paralysis of the respiratory muscles (myasthenia gravis, poliomyelitis). The resultant hypoventilation leads to a reduction of the alveolar oxygen tension and an elevation of the alveolar carbon dioxide tension. In turn, these aberrations initiate mechanisms whereby pulmonary vascular resistance is increased and pulmonary hypertension ensues. Alleviation of the hypoventilatory state leads to parallel reversal of pulmonary hypertension.[7,8]

The "organic" form of increased pulmonary "arteriolar" resistance is the result of marked decrease in the cross-sectional area of the pulmonary capillary bed. This may follow extensive pulmonary resection or substantial reduction in the functioning vascular area consequent to multiple pulmonary emboli,[9] tuberculosis, sarcoidosis,[10,11] Hamman-Rich syndrome, silicosis,[12] and berylliosis.

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In these states, despite normal ventilation, organic restriction of the pulmonary vascular bed results in an increased and fixed pulmonary resistance. This heightened, rigid resistance to flow may express itself as pulmonary hypertension at rest, or, with less extensive compromise, as pulmonary hypertension only during exercise.

This relationship between restriction of the capillary bed and cor pulmonale has been noted by others.[13] However, in approaching such states, the cardiologist and pulmonary physiologist have followed separate paths, each centering attention upon the specific cardiac or pulmonary aspects of capillary restriction.

Independently, the relation of pulmonary vascular limitation to the "cardiac" entity of cor pulmonale and the "pulmonary" disorder labeled as diffusion insufficiency have been well established. However, on the basis of such divided study, the suggestion currently persists that decrease in the pulmonary capillary bed may progress to the point of pulmonary hypertension, while the arterial blood gas values remain normal.[14] It is our contention that pulmonary hypertension of this type does not occur without the characteristic aberration of arterial gas values which defines the coexistence of a diffusion insufficiency for oxygen in the lung.

Through combining "pulmonary" and "cardiac" study techniques, we shall establish that restriction of the capillary bed is not only a major etiologic factor in cor pulmonale, but also results in simultaneous development of "diffusion insufficiency" for oxygen in the lung. This cardiopulmonary relationship has not been recognized previously.

CASES

Ten patients with various clinical disorders are presented in this study. Selection was made on the basis of prior studies which had demonstrated the existence of a pulmonary diffusion insufficiency for oxygen in each instance. Such a defect was established by (1) demonstration of a wide or high normal alveolo-arterial oxygen gradient at rest, which increased to pathologic values with exercise, and (2) exclusion of the presence of an abnormal venous admixture.

METHODS

In nine patients, concomitant pulmonary function and cardiac catheterization studies were performed, both at rest and exercise. In the tenth patient, the same procedure was followed with the exception that catheterization during exercise was not done.

Patients were catheterized from the left arm, under fasting conditions in the usual manner. Oxygen uptake, CO_2 output, minute ventilation and respiratory rate were measured either with the Pulmotest, a closed-system respirometer with automatic oxygen stabilizer, or by analyzing expired gases, with the patient breathing room air. Pressures in the pulmonary artery and the brachial artery were measured with Statham strain gauge manometers and were registered simultaneously in an Atlas 6-channel photoelectric writer. Exercise tests were performed with a Fleisch Ergostat for 10 minutes at a level compatible with the patient's maximum ability. Blood was collected in a steady state, never earlier than 8 minutes after the onset of exercise. Blood was analyzed for oxygen using an improved Haldane apparatus,[15] permitting double checks for content and capacity in one procedure. CO_2 in the plasma was analyzed with the Van Slyke apparatus. The pH was measured in a glass electrode at 37° C. and a Methrohm Potentiometer with an accuracy of $\pm$ 0.005 units. The pCO_2 was calculated from the Hasselbalch-Henderson equation using a pK′ of 6.11. The alveolar air equation was used to determine the alveolar pO_2. Cardiac output was calculated by the direct Fick principle. Pulmonary "arteriolar" resistance and right ventricular work were calculated by the following formulas:

TABLE I

		V_{O_2}	O_2CAP.	BRACHIAL ARTERY					p_AO_2	A-a	PULMONARY ARTERY					PAm	PCm	RAm	C.O.	PAR	RVW	PULSE
				O_2SAT.	p_aO_2	pH	pCO_2	BAm			O_2SAT.	p_vO_2	pH	pCO_2	PA							
1. C.C. 43♀	Rest	200	16.8	91.0	62	7.36	34.6	90	101	39	70.0		7.36	38.9	25/12	18	4	1	5.7	195	1.30	88
diffuse pulm. sarcoidosis	30 Watt	630		87.0	56	7.38	32.4	80	109	53	46.6		7.38	35.3	40/12	24	4	1	9.25	175	2.85	108
2. H.E. 32♂	Rest	195	17.5	96.2	87	7.39	36.0		99	12	72.0	40	7.33	42.6	30/10	18	4	1	4.6	245	1.05	83
cystic lung disease	80 Watt	995		92.5	71	7.35	33.5		108	37	40.6	26	7.23	56.8	60/20	33	5	2	11.0	205	4.60	144
3. M.H. 46♂	Rest	235	20.4	92.3	68	7.38	42.2		91	23	65.0	35	7.37	44.0	30/12	18	6	3	4.25	225	.85	62
pulm. tuberculosis	45 Watt	860		78.7	48	7.32	45.8		100	52	40.0	25	7.27	57.3	60/25	37	6	3	11.0	225	5.1	106
4. W.W. 42♀	Rest	205	19.0	94.0	78	7.35	36.5		96	18	62.1	34	7.35	43.3	30/15	20	4	3	3.4	375	.75	72
cystic lung disease	70 Watt	890		79.5	49	7.33	37.0		100	51	37.2	23	7.28	47.8	60/45	42	5	3	11.0	270	5.85	112
5. S.R. 34♂	Rest	290	20.5	80.9	48	7.39	35.2	100	100	52	65.5		7.37	39.2	65/30	42	6	2	9.2	315	5.0	110
pulm. fibrosis	40 Watt	785		46.1	26	7.35	38.6	109	105	79	11.6		7.32	40.9	95/40	60	8	2	11.2	370	8.85	138
after 6 weeks prednisone	Rest	220	20.1	93.6	73	7.43	33.9	80	100	27	72.7	38	7.38	39.7	40/18	22	4	2	5.25	275	1.45	80
	90 Watt	1150		78.5	43	7.39	31.2	100	109	66	22.6		7.34	35.7	80/35	50	5	2	10.3	350	6.72	108

6. R.F. 53♂ prim. pulm. hypertension	Rest 100 Watt	160 1200	20.0	91.3 82.9	65 52	7.39 7.30	37.6 39.9	98 125	96 102	31 50	70.3 21.1	40	7.36 7.25	43.5 51.0	60/10 70/25	36 55	8 7	2 2	3.8 9.7	590 400	1.75 7.0	56 106
7. G.E. 63♂ pulm. fibrosis	Rest 40 Watt	195 550	19.7	93.8 86.5	75 53	7.37 7.37	37.0 36.0	92 98	97 105	22 52	64.8 35.8		7.36 7.32	38.2 41.3	45/20 60/25	27 35	5 5	2 2	3.4 5.5	520 435	1.15 2.5	82 108
8. M.H. 62♂ prim. pulm. hypertension	Rest 80 Watt	270	19.0	88.7 82.1	58 48	7.39 7.36	35.1 28.5	85	112 120	54 72	56.3		7.37	37.7	60/20	40	10	2	4.4	545	2.3	76
9. E.W.* 50♂ I-A septal defect. Sec. pulm. hypertension	Rest 30 Watt	245 625	21.0	88.7 80.2	56 47	7.39 7.37	27.6 26.0	100 110	107 115	51 68	59.5 30.3	33	7.38 7.32	36.4 42.5	70/30 100/50	50 66	10 12	2 2	4.0 5.95	800 725	2.6 5.2	80 110
10. S.E. 50♂ prim. pulm. hypertension	Rest 35 Watt	200 600	14.6	93.6 87.4	72 55	7.37 7.35	38.3 39.6	98 122	96 102	24 47	40.0 9.6		7.37 7.33	41.0 46.1	55/25 90/50	39 70	5 5	2 2	2.55 5.2	1065 1000	1.3 4.8	88 120

*In Patient No. 9 arterial blood was collected from the pulmonary vein instead of the brachial artery.

V_{O_2}—Oxygen uptake in c.c. per minute.
O_2cap.—Oxygen capacity in volume per cent.
O_2sat.—Oxygen saturation per cent.
pO_2—Oxygen tension in mm. Hg.
pCO_2—CO_2 tension in mm. Hg.
BAm—Brachial artery mean pressure in mm. Hg.
p_AO_2—Alveolar oxygen tension in mm. Hg.
A-a—Alveolo-arterial oxygen tension gradient in mm. Hg.
PA—Pulmonary artery pressure in mm. Hg.
PAm—Pulmonary artery mean pressure in mm. Hg.
PCm—Wedge pressure in mm. Hg (mean).
RAm—Right auricle mean pressure in mm. Hg.
C.O.—Cardiac output in liters per minute.
PAR—Pulmonary arteriolar resistance in dynes sec. cm.$^{-5}$
RVw—Right ventricular work in Kg. per minute.
pvO_2—Mixed venous oxygen tension in mm. Hg.
P_aO_2—Arterial oxygen tension in mm. Hg.

Pulmonary "arteriolar" resistance* =

$$\frac{PA_m - PC_m}{C.O.} \times 80 \text{ dynes-sec.-cm.}^{-5}$$

Right ventricular work = $\frac{13.6 \times C.O. \times (PA_m - RA_m)}{1000}$ Kg. m./min.

PAm = Pulmonary artery mean pressure in mm. Hg; PCm = Wedge pressure in mm. Hg; RAm = Right auricular mean pressure in mm. Hg; C.O. = Cardiac output in liters per minute.

RESULTS (See Table I)

1. *Alveolar Ventilation.*—Alveolar ventilation is seen to be normal or increased, as evidenced by the normal or decreased arterial pCO_2 values.

2. *Mean Pulmonary Capillary Pressure.*—Mean pulmonary capillary pressure is within normal limits in all patients.

3. *Pulmonary "Arteriolar" Resistance.*—At rest, pulmonary "arteriolar" resistance was either abnormally high or at the upper limits of normal. With exercise, this resistance is seen to remain *fixed*, this being in contrast to the normally observed fall in resistance with exercise.[16,17] The highest values are found in Cases 9 and 10 which represent instances of primary and secondary pulmonary hypertension.

4. *Mean Pulmonary Artery Pressure.*—At rest, patients demonstrated mean pressures either at the upper range of normal or elevated above normal. With exercise, the mean pulmonary artery pressure demonstrates a linear rise as the cardiac output increases. (Fig. 1 presents graphically this mathematical relationship between pressure, flow, resistance, and work.)

5. *Alveolo-Arterial Oxygen Tension Gradient.*—At rest, the gradient is significantly elevated in all but 2 instances (Cases 2 and 4). With exercise, however, this gradient increases markedly in all patients and is reflected in a desaturation of the arterial blood. The increases in gradient which occur here are far above those which are seen normally with exercise, and cannot be accounted for on the basis of an increase in shunt. It is of interest to note the low levels to which mixed venous saturation descends with exercise, reaching as low as 9.6 per cent in Case 10.

6. *Right Ventricular Work.*—The work of the right ventricle is at high normal or definitely elevated levels in all patients at rest. With exercise, it is seen to mount to abnormal levels, rising in exponential fashion with increase in cardiac output.

COMMENT

The rise of pulmonary artery pressure with increased cardiac output, in the face of a fixed vascular resistance, implies that the velocity of blood flow through the pulmonary capillary bed must be heightened. The widening of the alveolo-arterial oxygen gradient with exercise, in the absence of a shunt, is characteristic

*The authors recognize that objections exist to the term "arteriolar resistance," with some preferring to use the term "pulmonary resistance." Also, some have objected to inclusion of the conversion factor of 80 in this formula. While both of these objections are valid, we have preferred to maintain the above terminology and formula in the interest of conformity with prior reports.

of a diffusion insufficiency.[18] Development of such a defect under these circumstances of rapid capillary blood flow indicates that perfusion of the alveolar bed is occurring with such rapidity that *contact time* between alveolus and capillary has been compromised to the point where it is insufficient to allow equilibration to take place between the alveolar oxygen tension and the capillary blood. Simultaneously, an increase of the work of the right ventricle occurs. Thus, the presence of a diffusion insufficiency for oxygen in the lung "signals," as it were, that capillary restriction is so extensive as to have fixed pulmonary "arteriolar" resistance, so that pulmonary hypertension and increased right ventricular work occur.

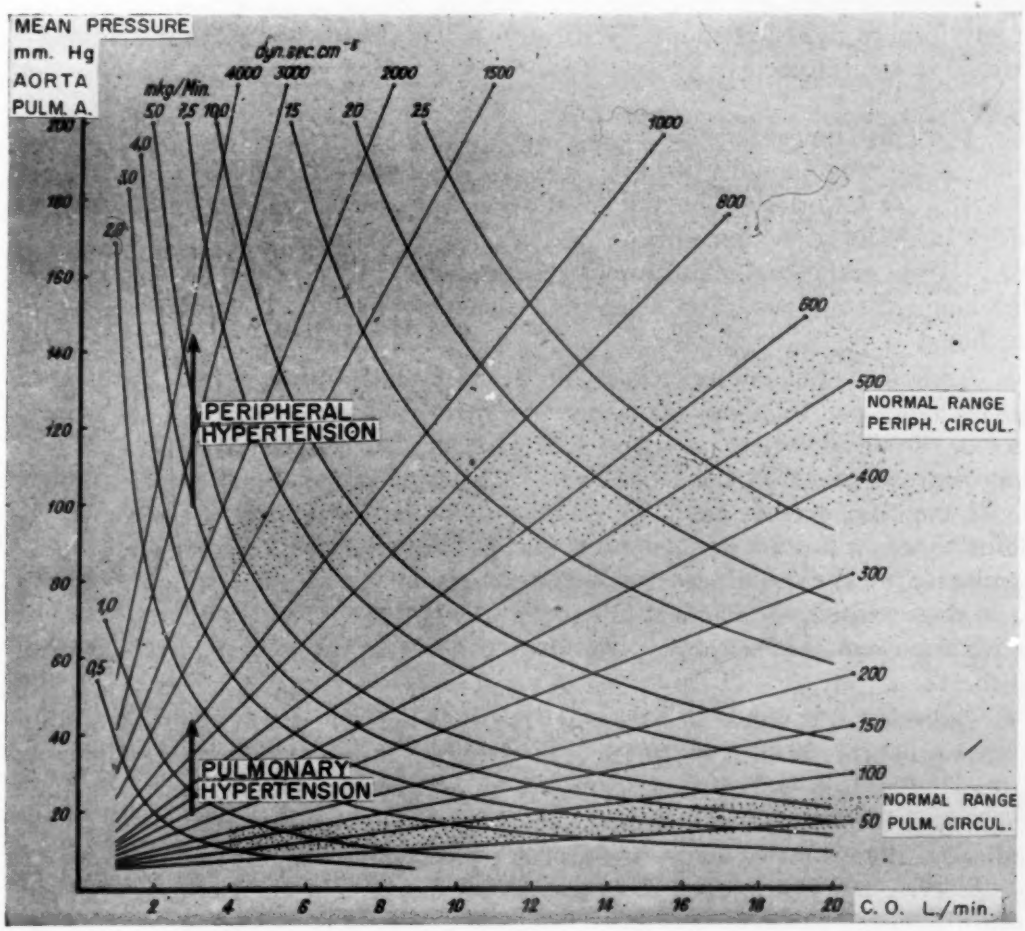

Fig. 1.—Graphic representation of the mathematical relationship between pressure, flow, resistance, and ventricular work.

DISCUSSION

It is a curious development that the "alveolar-capillary membrane," which traditionally has been the barrier between the provinces of cardiology and pulmonary physiology, now appears to form a strong link between these two discip-

lines. Indeed, as the above data indicate, the phenomenon of diffusion across this membrane, once a "pulmonary" problem, has now become a process of considerable interest to the cardiologist, for it is inseparable from such basic "cardiac" problems as cor pulmonale and alterations in pulmonary vasculature. Therefore, as a preface to further definition of the hemodynamic implications of "diffusion insufficiency," it would seem necessary first to review briefly the development of this concept, for it is not one with which the cardiologist is likely to be familiar.

"Diffusion insufficiency for oxygen" implies simply that there is a failure of equilibration between the oxygen tension in the alveolus and that attained by the capillary blood in its transit past the alveolar space. Thus, a difference, or "gradient," develops between alveolar and endcapillary oxygen tension which is reflected in an abnormal alveolo-arterial oxygen tension gradient, in the absence of any form of right-left shunt. With sufficient widening of the "A-a gradient," arterial desaturation may proceed to a level at which cyanosis is clinically detectable.

The first clinical suggestion that such a diffusion insufficiency for oxygen might occur was made by Brauer[19] during an epidemic of influenzal pneumonia in 1918. This worker noted the development of cyanosis in certain individuals which made its appearance before well-defined evidence of pneumonia was present. He hypothesized that this early appearance of cyanosis was due to the development of an alveolar "membrane" which impeded passage of oxygen into the blood.

Aside from this one brief flash of clinical interest, however, the problem of gas exchange had been, and continued to remain for a number of years, the province of the physiologist. Workers such as Bohr,[20] Barcroft,[21] Krogh,[22] and Haldane[23] strove to clarify the factors governing the passage of gases across the alveolar-capillary membrane. Douglas[24] contributed the important concept that diffusion was a process distinct from ventilation and could, therefore, lead independently to abnormalities of gaseous exchange. However, despite the significant theoretical and technical advances made by the physiologist, the problem of diffusion remained a hazy area of little concern to those interested in clinical medicine.

Indeed, it was not until the late 1940's that the concept of diffusion insufficiency was brought into sharp focus through the efforts of Lilienthal, Riley and others.[25-28] These workers, combining the use of certain fundamental principles delineated earlier by Bohr, Krogh, and Barcroft with newer methods of study, indicated that transfer across the alveolar membrane was not only a measurable process, but also played a significant role in certain clinical states.[29] The term "diffusing capacity" became popularized, and determinations of this "capacity" were made for oxygen and carbon monoxide.

It soon became evident, however, that "diffusing capacity," when measured at rest, was a relative value of limited significance. Riley and co-workers,[30,33] as well as Filley, MacIntosh, and Wright[31] demonstrated that it could be altered markedly by exercise and suggested the more dynamic entity of "maximum diffusing capacity" as a measurement of greater meaning. Though these workers indicated that alterations in pulmonary capillary area significantly influenced

"diffusing capacity," no experimental definition of this circulatory factor was attempted.

Indeed, the role of pulmonary vascular alterations was neglected as the theory and terminology of diffusion insufficiency developed further. The term "alveolo-arterial oxygen gradient" or "A-a gradient," popularized by Riley, became recognized as the focal point of diffusion abnormalities. As mentioned above, this gradient, in the absence of shunt, gives a rough approximation of the degree of diffusion insufficiency which exists, as its value represents the degree of "failure of equilibration" between alveolar and capillary oxygen tensions.

In seeking to explain those situations in which diffusion of oxygen was impaired, the term "alveolar-capillary block" soon came into common parlance.[34] This phrase carried the strong implication that the predominant defect in such states was the presence of some pathologic anatomic structure interposed between alveolus and capillary, i.e., a "thickened" alveolar-capillary membrane.

In invoking this "membrane theory," medicine once again demonstrated its tendency to define physiologic entities on the basis of demonstrable anatomic lesions. Such an approach, in the case of diffusion insufficiency, has led to a striking neglect of the other major factor involved in the process of diffusion, namely, pulmonary capillary dynamics.

To clarify the role played by circulatory changes in diffusion insufficiency, let us refer briefly at this point to the following formula which defines those factors involved in the diffusion of gases across a membrane:

$$V = \frac{k\,(P - P') \times S \times t}{d}$$

With specific reference to the lung and oxygen diffusion, V represents that volume of oxygen which diffuses under the influence of an oxygen tension difference (P - P' in mm. Hg) across the alveolar capillary membrane; k is a constant dependent upon molecular weight and solubility of oxygen in the membrane; S represents the surface; t indicates the time allowed for equilibration along the membrane between alveolus and capillary; and d is the distance between alveolus and hemoglobin molecule.

As one examines this formula, it becomes readily apparent that previous approaches to the problem of diffusion have laid virtually exclusive stress upon the factor d or the *membrane factor*. Yet, it is quite evident that gaseous diffusion may be affected by the factor t, i.e., the time of contact allowed between alveolar gas and capillary blood.[35,36] Why, then, has the term "alveolar-capillary block" gained general acceptance, suggesting as it does that it is essentially the thickness of the alveolar-capillary "membrane" which is the cause of diffusion abnormalities?

The answer to this question is the focal point of the present discussion. Simply put, the answer is that the extent of the interdependence between cardiac and pulmonary phenomena has not been fully explored, although the need for such an integration of data has been appreciated for sometime. Cournand, through the technique of right heart catheterization (Forsmann), took the first step toward this vital correlation of cardiac and pulmonary function. However, to date, despite possession of the necessary techniques, intensive application of

this correlative approach has been minimal. In the case of diffusion insufficiency, it is only by such simultaneous cardiac and pulmonary study that the "time of contact" can be recognized as a central feature in this disorder. This is so because the "time of contact" does not exist as a palpable, anatomic barrier which can be identified as a "thickened membrane." Rather, it is a physiologic "barrier," related to circulatory dynamics within the pulmonary bed, and can be identified only by study of dynamic, physiologic events.

With these basic concepts in mind, let us now consider the problem of "diffusion insufficiency" with the aid of this comprehensive experimental approach.

Normally, in the resting state, only a portion of the available capillary bed within the lung is perfused. The result is a relatively high resting "arteriolar" resistance (150-200 dynes sec. cm.$^{-5}$). With exercise, more capillaries are opened and the resistance often falls to levels below 100.[16,17] Operation of this mechanism for decrease in resistance allows the pulmonary artery pressure to be maintained within normal limits despite a threefold or fourfold increase in the pulmonary blood flow (see Fig. 1).

However, there are a number of instances in which the pulmonary capillary bed can suffer marked reductions in capacity. As mentioned previously, extensive resection of the lung, various forms of interstitial fibrosis, and multiple pulmonary emboli are among the entities which can produce considerable reduction in the capillary bed.

When such restrictions of the vascular bed exist, a high percentage of available channels are being utilized for perfusion at rest. With exercise, the normal mechanism for decreasing pulmonary vascular resistance, namely, the opening of resting capillaries, can no longer be brought into play. If a vascular bed with such a fixed resistance is called upon to accept an increased pulmonary blood flow, its only available mode of adjustment lies in the acceleration of flow through those capillaries which remain. When such acceleration reaches a critical level, contact time between alveolus and blood becomes insufficient to allow equilibration between alveolar and capillary oxygen tensions. The result is a widening of the A-a oxygen tension gradient and the development of arterial unsaturation, i.e., a diffusion insufficiency is noted. That the critical level has been attained in this fixed resistance system is signified simultaneously by a linear rise in the pulmonary arterial pressure as the pulmonary blood flow mounts. It is clear that under these circumstances the attainment of full arterial saturation through high oxygen breathing would be without effect on the elevated pulmonary artery pressure.

Furthermore, of central importance is the realization that, *if diffusion were a pure "membrane" problem, this correlation between fixation of pulmonary "arteriolar" resistance, elevation of pulmonary arterial pressure, and widening of the A-a oxygen gradient would not be found.* The experimental data presented here confirm, in each instance, that these relationships do hold.

It is to be emphasized that we do not deny the possibility that a true "membrane factor" may exist in certain instances of diffusion insufficiency. However, in all the patients reported here, the development of a diffusion insufficiency, in the face of a fixed pulmonary "arteriolar" resistance and normal capillary pres-

sure, is characterized not only by a widened A-a gradient, but by an elevation of the pulmonary artery pressure as well. Thus, it would appear that reduction in alveolar-capillary "contact time" plays a major role in what has been labeled previously as "alveolar-capillary block."

Demonstration of these cardiopulmonary events has a number of significant implications for the cardiologist. Primary among these is the close relationship between diffusion insufficiency and cor pulmonale. As has been demonstrated above, pulmonary artery pressure and right ventricular work are uniformly elevated in individuals with diffusion insufficiency at rest. Any further increase in pulmonary blood flow leads to an exponential rise in right ventricular work. Thus, the presence of diffusion insufficiency at rest immediately implies that fixation of pulmonary "arteriolar" resistance, pulmonary hypertension, and increased levels of right ventricular work coexist. Further, if diffusion insufficiency is absent at rest, but develops with exercise, one can define rather accurately the level of exercise at which the individual under study will develop pulmonary hypertension and increased right ventricular work.

The therapeutic implications of these physiologic data are clear. In the face of unalterable anatomic vascular changes, we must resort to purposeful physiologic alterations in order to achieve real therapeutic benefit for such patients. In patients who manifest diffusion insufficiency only when exertion demands an elevation of pulmonary blood flow, limitation of activity below such levels will prevent recurrent episodes of increased right ventricular work that may eventually lead to right ventricular failure. Less fortunate are those with diffusion insufficiency at rest. The only alteration which could aid these latter individuals would be a lowering of the pulmonary blood flow, as has been demonstrated.[37] As pulmonary blood flow is reduced, the patient benefits doubly, because (1) as perfusion of the capillary bed may proceed at a slower velocity, more adequate contact time is allowed between alveolus and blood for diffusion of oxygen, and (2) simultaneously, pulmonary artery pressure and right ventricular work are decreased.

To date, only two methods are available for achieving this goal of reduced pulmonary blood flow, with both being dependent on a decrease in the cardiac output. The first method is the imposition of marked restriction of bodily activity. This reduction of such individuals to invalidism is currently the only course offered to patients by the physician. An alternative approach is the utilization of certain hypotensive agents which can bring about a lowering of the cardiac output. Trial of this form of treatment, wherein also lies further verification of the importance of contact time, will form the substance of a subsequent report.[38] A third avenue of approach, little explored as yet, would be the use of such agents as radioactive iodine in an attempt to decrease requirements of cardiac output.

There is a second major implication of the present studies of diffusion insufficiency. This relates to the ability of the method to define the presence of a "fixed pulmonary arteriolar resistance" in individuals studied. In numerous patients with forms of congenital or acquired heart disease that are technically amenable to surgical correction, the presence of a fixed pulmonary hypertension

may have considerable bearing on the ultimate success of the surgical attack. The extent to which this pulmonary hypertension is reversible is, therefore, a topic of much current debate.

While the cardiologist and surgeon would like to identify preoperatively those individuals with a high, fixed pulmonary vascular resistance, they have been unable to do so accurately through previously available techniques. However, utilization of the principles delineated by this report can now make such information available. For if a given subject has demonstrable a diffusion insufficiency at rest, the implication is clear that pulmonary "arteriolar" resistance is fixed. If the patient develops diffusion insufficiency with exercise, the expansile capacity of the pulmonary vascular tree is defined by the cardiac output at this point. Finally, if diffusion is normal at rest and during considerable exercise, one can be assured that the pulmonary vascular bed has retained its expansile capacity, i.e., is not a fixed resistance system over a wide range of cardiac output. With such information at hand, operation can be considered with a more precise forehand knowledge of the state of the pulmonary vascular bed.

Thus, somewhat unexpectedly perhaps, the present studies of a "pulmonary" abnormality—diffusion insufficiency for oxygen—have made available techniques of evaluation which may prove of considerable value to the cardiologist.

SUMMARY

The relationship between restriction of the pulmonary capillary bed, pulmonary hypertension, and diffusion insufficiency for oxygen has not been appreciated previously. Studies are presented which demonstrate that in all patients who develop pulmonary hypertension on the basis of restriction of the pulmonary capillary bed, a diffusion insufficiency for oxygen coexists, because of an inadequate alveolar-capillary contact time. This integral relationship between diffusion insufficiency and basic pulmonary hemodynamic events has both diagnostic and therapeutic implications for the cardiologist.

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THE EFFECT OF PRISCOLINE* (TOLAZOLINE HYDROCHLORIDE) ON THE ARTERIAL PRESSURE PULSE CONTOUR IN AORTIC STENOSIS

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DIRECT arterial pressure tracing is frequently a reliable guide in the diagnosis of aortic stenosis. The characteristic changes are prolonged crest time, anacrotic phenomena (anacrotic break, notch, wave, or vibrations), and small pulse pressure.[1] Hence, the peripheral arterial pressure tracing resembles the central pulse contour.[2-6] In many cases of aortic stenosis, however, the peripheral pulse contour remains normal.[7,8] In some of these cases the performance of the Valsalva maneuver may cause transient appearance of a stenotic pulse wave pattern and is, therefore, of value in detecting mild aortic stenosis.[3] Other techniques are also used to obtain a characteristic pressure pulse contour.[9,10]

In this study an attempt was made to add an aid in diagnosing aortic stenosis in doubtful clinical cases with normal resting arterial pressure tracings. For this purpose Priscoline (tolazoline hydrochloride) was administered intra-arterially, in order to eliminate peripheral reflected waves, which are partly responsible for the distortion of the central pulse contour during its travel to the periphery.

MATERIAL AND METHOD

Thirty-eight patients with various valvular heart diseases, and 12 normal individuals were chosen for this study. The clinical diagnoses were based upon the history and physical findings, and upon electrocardiographic and x-ray examinations. In all subjects direct arterial pressure tracings were obtained through a Cournand needle (No. 18) inserted into the brachial artery. A Sanborn Electromanometer was used, and the tracing was recorded on a Sanborn Twin-Viso-cardiette at 25 mm. per second paper speed. The second lead of the electrocardiogram was recorded simultaneously. Direct arterial pressure tracings were obtained before, during, and after the Valsalva maneuver. When the original resting curve contour reappeared, the recording was interrupted and 15 mg. of Priscoline† was rapidly injected, using a three-way stopcock, into the brachial artery. The recording was then continued for about 30 seconds, and the Valsalva maneuver was again performed.

Analysis of the pressure pulse contour and measurement of the crest time (from the foot of the ascending limb to the highest point of it) were made on the following sections of the tracings: (a) resting pulse tracing, (b) 10 seconds after Valsalva maneuver, (c) 10 seconds after administration of Priscoline, and (d) 10 seconds after the postinjection Valsalva maneuver.

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*Registered trademark.

†2-benzyl-4, 5-imidazoline hydrochloride.

RESULTS

The 50 individuals studied were divided into 4 groups, according to their clinical diagnoses.

Normal (Figs. 1, 2, 3).—In the group of 12 normal individuals, the pulse contour at rest was normal and the crest time was not longer than 0.12 second. After performance of the Valsalva maneuver the usual response appeared, i.e., bradycardia, overshoot, increased pulse pressure, and in some cases the appearance of reflected waves on the descending limb. There was no change in the ascending limb of the tracing. These alterations disappeared usually in

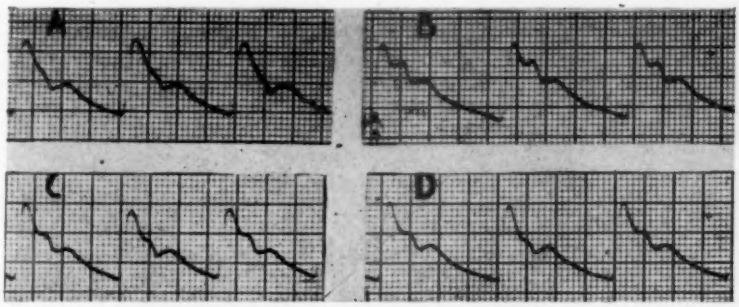

Fig. 1.—Direct peripheral arterial pressure tracing of normal subject at rest (*A*), after Valsalva maneuver (*B*), after intra-arterial injection of Priscoline (*C*), and following a postinjection Valsalva maneuver (*D*). Note absence of significant change in the tracings.

Fig. 2.—Direct peripheral arterial pressure tracing of normal subject at rest (*A*), after Valsalva maneuver (*B*), after intra-arterial injection of Priscoline (*C*), and following a postinjection Valsalva maneuver (*D*). Note absence of significant change in the tracings.

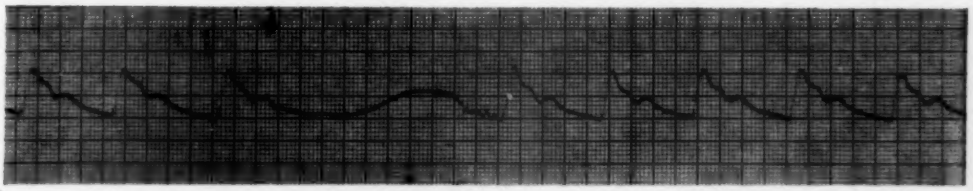

Fig. 3.—Direct peripheral pressure tracing of normal subject. Administration of 15 mg. Priscoline is indicated by the arrow. Note absence of significant change in the pulse contour.

from 30 to 60 seconds. Following the administration of Priscoline, no significant change occurred either in the appearance of the ascending limb or in the crest time. The vasodilatation produced by this drug generally caused slight decrease in systolic pressure, sometimes resulting in a rounded curve. The performance of the additional Valsalva maneuver after the injection did not cause any significant change in contour or crest time in addition to those which occurred in the post-Valsalva phase before the injection.

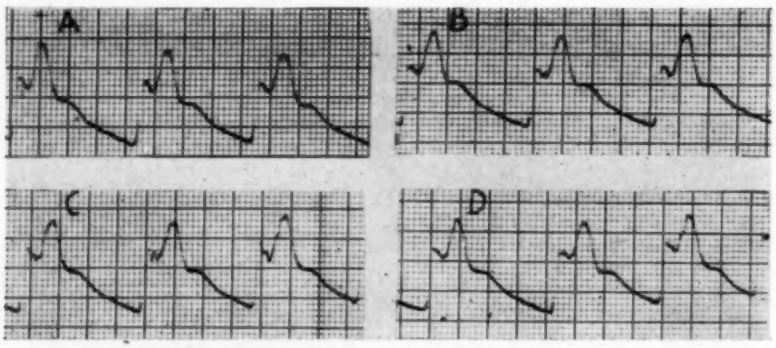

Fig. 4.—Direct peripheral arterial pressure tracing of a patient with advanced aortic stenosis. Marked anacrotic notch and prolonged crest time at rest (*A*). No significant change after Valsalva maneuver (*B*), after injection of Priscoline (*C*), and following a postinjection Valsalva maneuver (*D*).

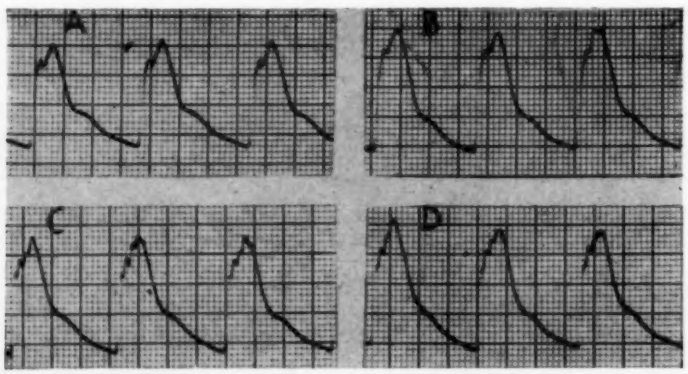

Fig. 5.—Direct arterial pressure tracing of a patient with predominant aortic stenosis accompanied by slight aortic regurgitation. High anacrotic notch and slightly prolonged crest time at rest (*A*), with no change after Valsalva maneuver (*B*). Administration of Priscoline causes appearance of small vibrations on the ascending limb (*C*); no additional change following the postinjection Valsalva maneuver (*D*).

Aortic Stenosis (Figs. 4, 5, 6, 7, 8, 9).—In this group, 11 patients were studied. Each of them had symptoms and signs of aortic stenosis. In 3 cases arteriosclerotic, and in 3 cases congenital origin was suspected (in one of these latter it was proved at autopsy). In 3 cases some regurgitation was present.

In 5 out of the 11 patients the contour and the crest time of the resting tracings were consistent with the clinical diagnosis. The crest time was prolonged, ranging between 0.20 and 0.26 second. In 3 of the cases the ascending limb was interrupted by anacrotic break or notch; in the other 2 the anacrotic limb was smooth. In the post-Valsalva period there was no significant change in the pulse

contour and crest time. Administration of Priscoline caused no change in contour or crest time, nor were they affected by the Valsalva maneuver performed after the injection.

The remaining 6 cases of aortic stenosis revealed normal pulse contour and crest time (0.08 to 0.14 second) at rest. In one of them the Valsalva maneuver itself caused lengthening of the crest time from 0.12 to 0.20 second, and the appearance of a well-marked anacrotic notch. Administration of Priscoline prolonged the crest time even more (0.23 second), while instead of an anacrotic notch, an anacrotic shoulder developed. The postinjection Valsalva maneuver did not alter this tracing. In the other 5 cases the Valsalva maneuver did not produce any change in crest time or in the anacrotic limb. In 3 out of these 5 cases, following the administration of the drug, anacrotic phenomena occurred

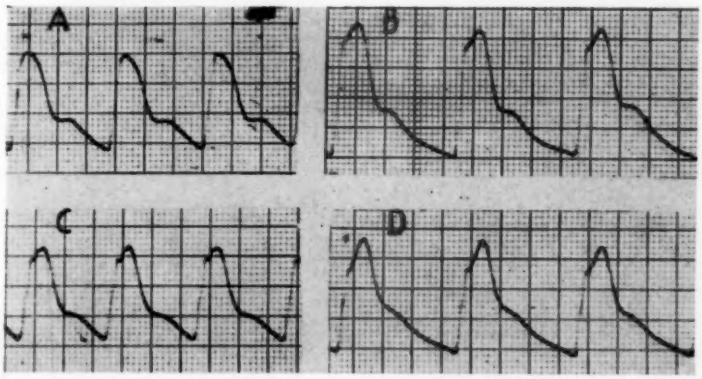

Fig. 6.—Direct arterial pressure tracing of a patient with aortic stenosis. The resting pulse contour and crest time are normal (*A*); after Valsalva maneuver anacrotic break and prolongation of crest time (*B*). Administration of Priscoline produces slight deviation of the anacrotic limb at a low position (*C*); no significant change following postinjection Valsalva maneuver.

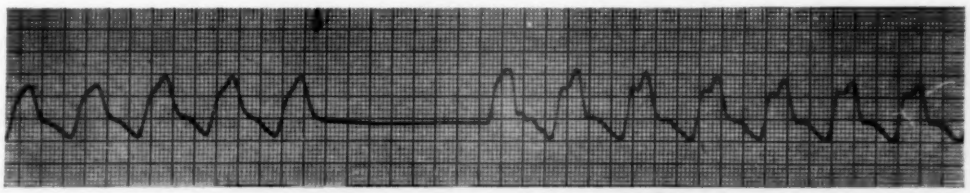

Fig. 7.—Direct peripheral arterial pressure tracing of a patient with aortic stenosis. Administration of Priscoline (↓) exaggerates the stenotic pattern.

Fig. 8.—Direct peripheral arterial pressure tracing of a patient with predominant aortic stenosis. Administration of Priscoline (↓) exaggerates the stenotic pattern.

(prolongation of the crest time in 1 case, anacrotic notch in 2 cases, and anacrotic vibrations in 1 other). A Valsalva maneuver performed 30 seconds later exaggerated the signs of aortic stenosis which had been evoked by administration of the drug. The fifth patient of this group, who had severe generalized arteriosclerosis, did not reveal changes in pulse contour or crest time after administration of the drug or after the postinjection Valsalva maneuver.

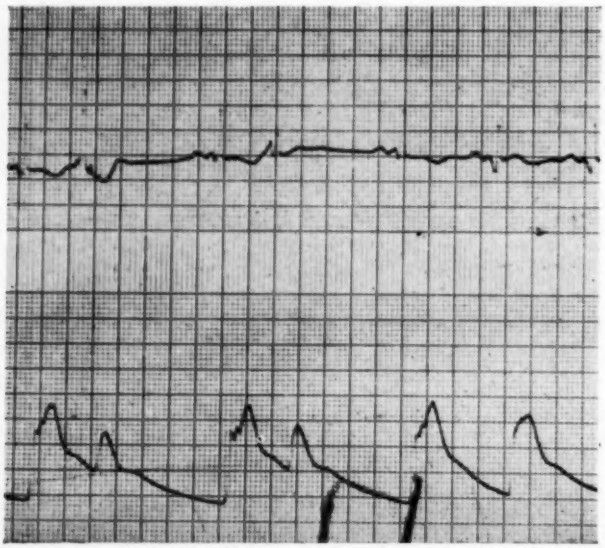

Fig. 9.—Direct peripheral arterial pressure tracing of a patient with aortic stenosis. The pulse contour of the normal beats exhibits small anacrotic vibrations and prolonged crest time, while these signs are absent in pulse contour of ectopic beats.

Suspected Aortic Stenosis (Figs. 10, 11, 12).—This group consisted of 18 patients in whom mild cardiac symptoms, presence of a basic systolic murmur, relatively low blood and pulse pressures, tall R waves in $V_{5,6}$, and slight enlargement of the left ventricle made the diagnosis of aortic stenosis probable but not definite.

The pressure pulse tracings of all these patients showed a normal resting contour with normal crest time (0.06 to 0.16 second), and there was no change in the anacrotic limb or crest time after the Valsalva maneuver. Administration of Priscoline failed to produce any effect on the contour of the pressure tracing or on the crest time. However, in 8 out of these 18 cases performance of the Valsalva maneuver after the injection of the drug caused definite changes, namely, anacrotic notch, shoulder, or vibration, with markedly prolonged crest time up to 0.25 second. In the remaining 10 cases even the postinjection Valsalva maneuver did not cause remarkable changes.

Combined Valvular Disease (Figs. 13, 14).—This group consisted of 9 patients. Seven patients had mitral stenosis, with suspected aortic stenosis in 3 of them. Two patients had aortic insufficiency. The resting arterial pressure tracing and that taken after the Valsalva maneuver revealed normal contour and crest time in the patients with mitral stenosis. In 4 patients the injection of Priscoline and the Valsalva maneuver thereafter did not cause the appearance of a curve of the

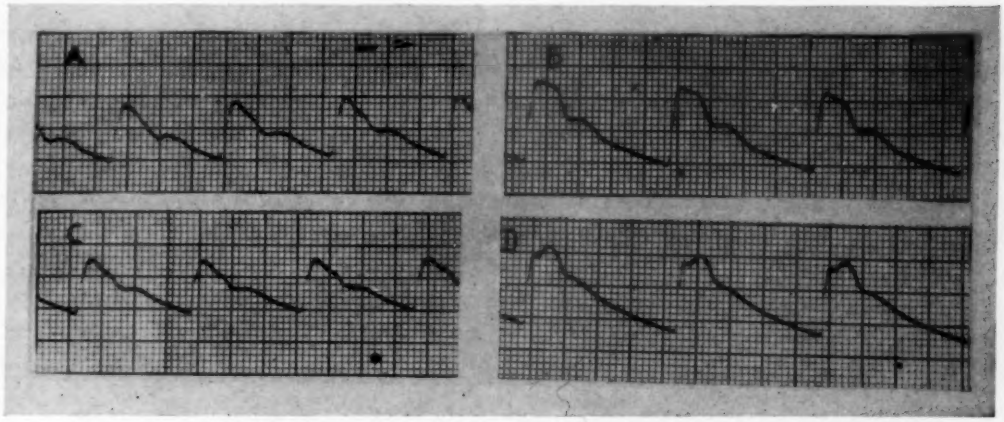

Fig. 10.—Direct peripheral arterial pressure tracing of a patient with suspected aortic stenosis. The anacrotic limb is smooth, the crest time is normal at rest (*A*). The Valsalva maneuver does not change the contour or the crest time (*B*). Administration of Priscoline does not alter the tracing significantly (*C*). The postinjection Valsalva maneuver produces marked anacrotic deviation and prolonged crest time (*D*).

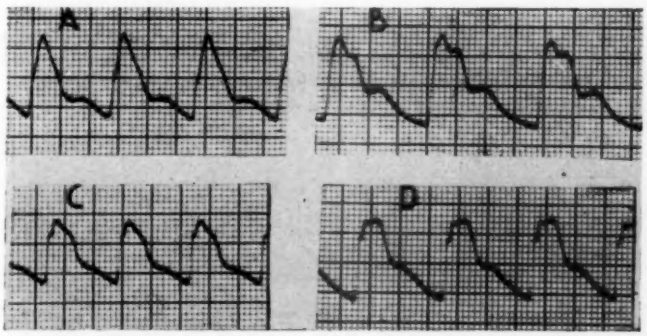

Fig. 11.—Direct peripheral arterial pressure tracing of a patient with suspected aortic stenosis. Slight anacrotic deviation and normal crest time at rest (*A*), and after Valsalva maneuver (*B*). Administration of the drug does not produce appearance of stenotic pattern (*C*), but after the Valsalva maneuver anacrotic phenomena and prolonged crest time are seen (*D*).

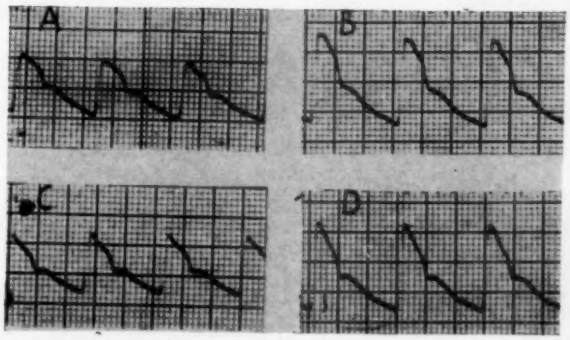

Fig. 12.—Direct peripheral arterial pressure tracing of a patient with suspected aortic stenosis. No signs of aortic stenosis are seen at rest (*A*), after Valsalva maneuver (*B*), after administration of Priscoline (*C*), and following the postinjection Valsalva maneuver (*D*).

aortic stenotic type. Of the 3 patients with mitral and suspected aortic stenosis, the injection of the drug in one case, and the postinjection Valsalva maneuver in another case caused the appearance of the stenotic pattern. In the third case no remarkable changes were observed. In 2 cases with aortic insufficiency the resting pressure tracing was characteristic for this lesion. Valsalva maneuver, injection of Priscoline, and postinjection Valsalva maneuver only exaggerated the pattern of insufficiency, without additional changes.

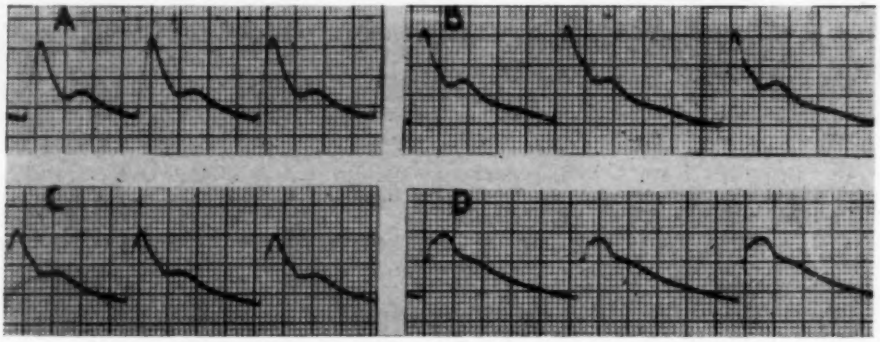

Fig. 13.—Direct peripheral arterial pressure tracing of a patient with mitral stenosis and suspected aortic stenosis. The pulse contour and crest time are normal at rest (*A*), and after Valsalva maneuver (*B*). Administration of Priscoline produces a slight anacrotic break (*C*), while following postinjection Valsalva maneuver the tracing resembles central pulse contour (*D*).

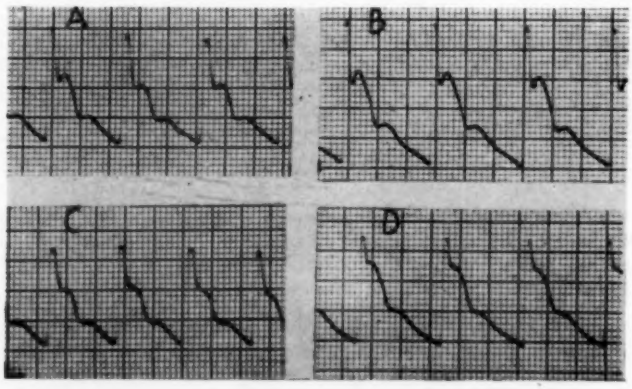

Fig. 14.—Direct peripheral arterial pressure tracing of a patient with aortic regurgitation. The pulse contour at rest is characteristic for this lesion (*A*). No significant change occurs after Valsalva maneuver (*B*), after administration of the drug (*C*), and following the postinjection Valsalva maneuver (*D*).

COMMENT

Peripheral arterial pressure pulse represents a transmitted central pulse curve, greatly distorted by the physical properties of the arterial system and by the summation of standing and reflected waves on it.[1,11] Dow[2] claimed that in aortic stenosis the force of the systolic ejection is so much reduced by the high resistance of the stenotic valve that no standing waves are generated in the arterial tree. Hence, the central pulse wave is transmitted to the periphery, producing the characteristic stenotic pattern.[2,3,4,7] Krocker and Wood[5] suggested that in

aortic stenosis, consequent to the reduced force of systolic ejection, the peripheral amplification of the central pulse is reduced. Moreover, it has been demonstrated in a mechanical model of circulation that it is not the degree of the stenosis that determines the pathognomonic pulse wave, but the impaired pumping action of the heart and/or altered peripheral vascular resistance.[12] In addition, the effect of changing stroke volume on the pulse contour was emphasized by Feil and Katz[1] in cases of aortic stenosis with atrial fibrillation.

It has been shown, however, that in many mild cases of aortic stenosis, the peripheral pressure tracing may be of normal contour, and thus does not help in diagnosis.[3,7,8] In these cases the performance of the Valsalva maneuver may be of aid. In the poststraining phase of this maneuver the increased venous return augments the amount of blood expelled from the heart. Since the force of the ventricular ejection is already partially spent in overcoming the resistance of the stenotic valve, this increased stroke volume causes a further deterioration of ventricular contraction, thus leading to the transient appearance of the central-like pattern in the peripheral artery.[3]

In mild cases of aortic stenosis, with apparently normal resting peripheral arterial tracing and without remarkable change after the Valsalva maneuver, the central factor, the ventricular ejection, is not impaired to such a degree as to cause characteristic changes in the peripheral artery. The contour of the peripheral arterial pressure pulse is determined by the vasomotor tone of the arterioles as well. Hamilton[13] demonstrated that administration of acetylcholine causes damping out of the reflected waves, and so the normal central pulse contour may be transmitted to the periphery without marked distortion. On the other hand, Alexander,[14] after administration of another vasodilating agent (adenylic acid), observed contour changes in the aortic pressure tracing, but no remarkable alterations appeared on the peripheral curve.

The administration of Priscoline in our study was based upon the assumption that in those cases of mild aortic stenosis where the impairment of ventricular systole is not severe enough to reduce the creation of reflected waves, vasodilatation by elimination of these waves will produce a peripheral pressure pulse contour which resembles the pathologic central pulse curve. Our observations indicate that in normal individuals administration of this drug does not produce transmission of the central pulse to the periphery. On the other hand, in cases of aortic stenosis with normal resting contour, its administration causes appearance of anacrotic phenomena and prolonged crest time in the peripheral pulse curve. It is suggested that the type and extent of the vasodilatation produced by the intra-arterial administration of Priscoline was unable to abolish the peripheral distortion of the central pulse in normal individuals. However, it was able to do so in cases of aortic stenosis with impaired ventricular ejection. This explanation is supported by the fact that in patients with advanced aortic stenosis, in whom the stenotic central pattern was already propagated to the periphery undistorted by reflected waves, vasodilatation either had no effect or exaggerated the signs of aortic stenosis.

In 8 out of 18 patients with clinically suggested aortic stenosis, but normal resting pressure tracing, administration of this drug caused the appearance of a

stenotic pattern in the peripheral artery only after performance of the post-injection Valsalva maneuver. We assume that, in addition to vasodilatation, the vigorous ventricular contraction in the poststraining phase was needed to transmit the central pulse-like contour to the periphery. The lack of response to both Priscoline and the subsequent Valsalva maneuver in 10 patients with the doubtful clinical diagnosis suggests that in these cases the existence of aortic stenosis is unlikely.

SUMMARY

In 38 patients and in 12 healthy individuals the contour of the direct arterial pressure tracing was studied. The tracings were taken at rest, after performance of the Valsalva maneuver, after intra-arterial injection of Priscoline, and after a postinjection Valsalva maneuver.

In healthy individuals administration of the drug did not cause transmission of central pulse to the periphery.

In 5 patients with aortic stenosis and pathognomonic resting pulse curve, Priscoline either had no effect or exaggerated the signs of stenosis in the pulse contour. In 6 patients with aortic stenosis and normal peripheral pressure tracings, administration of the drug provoked the appearance of a stenotic pattern.

In 8 out of 18 patients with suspected aortic stenosis, with normal pulse tracing both at rest and after Valsalva maneuver, administration of Priscoline and the subsequent Valsalva maneuver produced the appearance of anacrotic phenomena and prolonged crest time in the peripheral arterial pressure tracing. In the remaining 10 patients of this group no such stenotic pulse pattern was produced by administration of the drug.

The value of the procedure in the diagnosis of aortic stenosis and the possible mechanism responsible are discussed.

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ADDENDUM

Since this article was submitted for publication, 50 additional pressure pulses were recorded using the above-described procedure. The results obtained in this series were similar to those reported above.

CLINICAL VALUE OF THE VENOUS PULSE

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AT THE beginning of the eighteenth century, Lancisi described in his classical book *Motus Cordis et Aneurysmatibus* a "systolic fluctuation" of the external jugular vein, easily seen in the neck in a patient with tricuspid insufficiency proved by the post-mortem examination. A century later the advent of the Chauveau and Marey[2] mechanical graphic recording method made possible the direct inscription of the venous pulse from the surface of the neck. Later on, several investigators studied this phenomenon with the above method, but the outstanding contributions were those of Potain,[3] who recognized the presystolic time and the auricular origin of the most important wave of the venous pulse. Finally, Sir James Mackenzie[4] settled the matter with the use of his classical polygraph method. He recognized 3 main waves, calling them *a*, *c*, and *v*, because they were the first letters of their anatomic origin: the right atrium, the carotid artery, and the right ventricle, respectively. After studying these findings, he discovered not only Lancisi's sign, which is known today as the positive or ventricular venous pulse, but also the most frequent disorder of the cardiac rhythm, that which was later called auricular fibrillation.

The appearance of clinical electrocardiography at the beginning of this century, with a simpler technique and interpretation, and greater diagnostic possibilities, has relayed phlebography to a secondary position in the clinical recognition of cardiac arrhythmias. On the other hand, the increasing ability to diagnose several of these arrhythmias by the examination of the radial pulse and heart sounds has led to a neglect of the inspection of the venous pulse in the neck, disregarding in this way its diagnostic value in other cardiac conditions, such as in tricuspid insufficiency and ventricular tamponade, both recognizable by one of the types of the pathologic venous pulse, the so-called positive or ventricular venous pulse.

It is true that when tricuspid regurgitation is present the positive venous pulse is easily mistaken for the carotid pulse, because both are systolic in time and both may be felt by the finger on the neck. Our experience with this subject, having been checked day after day by phlebography, has convinced us that it is quite possible to make clinical recognition of the positive venous pulse, if we add, however, some other facts to the classical criteria. It is the purpose of this paper to emphasize the clinical value of the venous pulse on the basis of this experience.

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METHOD

In order to present these findings in an objective way, graphic recordings or phlebograms will be used, but it must be emphasized that one of the waves of the phlebogram, the *c* wave, is not seen in the neck, either because it is an artefact or because it is beyond the range of visual acuity.

In addition to phlebograms, recordings obtained during catheterization of the heart and of the jugular vein will be shown, in order to display artefacts inherent to the reception system of the phlebograph.

PHYSIOLOGIC VENOUS PULSE

In normal conditions, and especially in the supine position with the head slightly elevated, pulsations of venous origin are observed at the lowest part of the neck, along the external jugular vein, or along the sternocleidomastoid muscle, that is, the projection of the internal jugular vein, more on the right than on the left side. These pulsations are visible but not palpable. During expiration, or with manual abdominal pressure, they are shifted headwards, while during inspiration and in the upright position, they are shifted towards the chest and may disappear behind the clavicles (Fig. 1).

In each cardiac cycle two waves are seen in the neck, one larger and presystolic, the atrial *a* wave, the other smaller and diastolic, the ventricular *v* wave. The *c* wave is not visible, either because it is an artefact of the phlebogram due to the adjacent carotid pulse picked up by the capsule or because of its small size.

According to classical criteria, diastolic timing of the venous pulse waves is elicited clinically by correlating it with the heart sounds or the radial or carotid pulses; the most accurate for this purpose, however, is the latter, as it succeeds the venous pulse in a perfect to-and-fro motion. This timing may be difficult to elicit with tachycardia. For these reasons it is the visibly successive coupling of the venous pulse waves which is the most important characteristic for its clinical recognition. Depending on the cardiac rate, and hence diastolic interval, two types of successive coupling may be seen in the neck: the ascending two-step stair, and the double independent waves (Fig. 2).

The ascending two-step-stair configuration in the sequence of two waves (the first smaller, followed by a second one which is larger) is followed by a quick collapse. It is seen in the neck with normal or rapid cardiac rates, because in these conditions diastole is not unduly long and the ventricular *v* wave is nearer to the following rather than to the preceding atrial *a* wave. That is to say, the visual image is thus: the smaller ventricular or *v* wave is seen first, and next, but in junction, is the larger atrial or *a* wave, followed by a quick downward systolic collapse.

The double independent wave configuration consists in two separated waves, but the visible coupling is just reversed; first the larger wave is seen and afterwards the smaller one. This configuration is found in low cardiac rates, where diastole is longer and the ventricular or *v* wave is nearer to the preceding rather than to the following atrial or *a* wave. The resulting visual image is this: the larger atrial or *a* wave is seen first, and next, but independently, the smaller ventricular or *v* wave, and afterwards follows the diastolic collapse.

As can be seen, the visual picture is reversed in the latter and is different

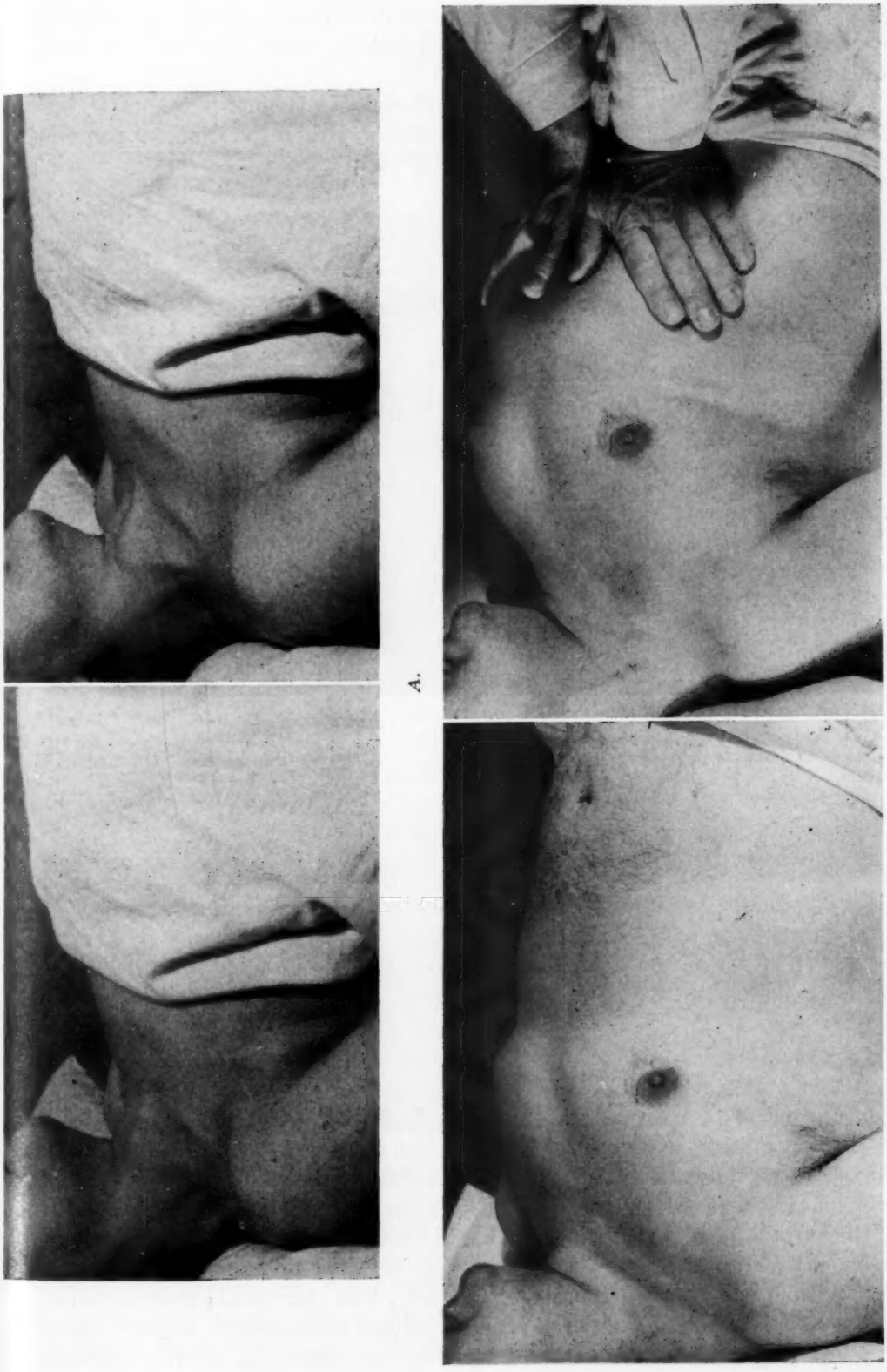
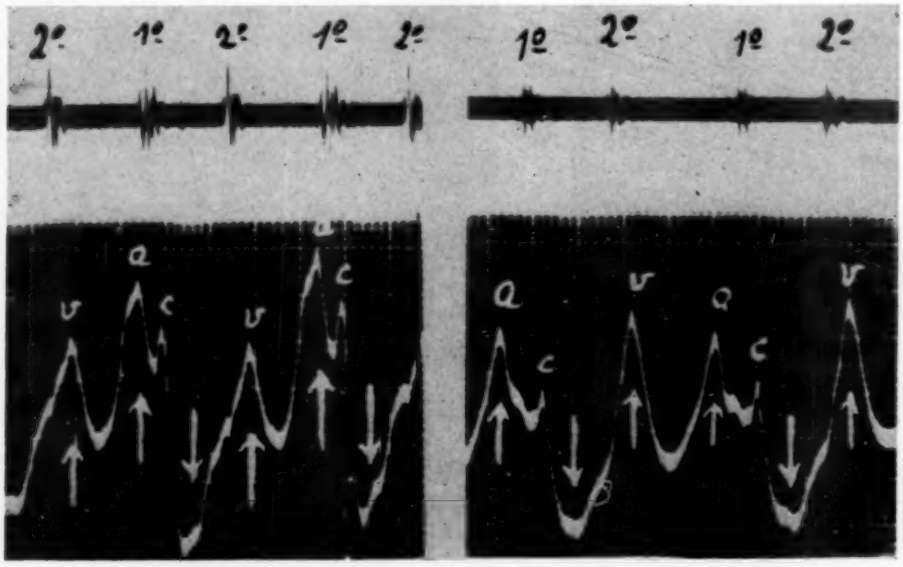


Fig. 1.—*A*, Left, inspiration; right, expiration: *B*, Left, without abdominal pressure; right, manual abdominal pressure (see text).

in both types of venous pulse. Their common character, however, is the presence of two waves, whether joined or independent, while the arterial pulse shows a single pulse wave.

All these distinctive qualities of the physiologic venous pulse, most important of which are its configuration and shifts with respiration, abdominal pressure, and decubitus, permit its diagnosis in health.



A. *B*

Fig. 2.—Simultaneous phonocardiogram and phlebogram. (*A*) Two-step-stair type; (*B*) double independent type waves.

PATHOLOGIC VENOUS PULSE

In certain clinical conditions the physiologic venous pulse suffers modifications of definite diagnostic value. Under these conditions it is known as a pathologic venous pulse. The following types may be distinguished: (a) positive venous pulse; (b) lack of pulsation or less frequency of rapid fluttering in an engorged external jugular vein; (c) absence of shifts with respiration; and (d) giant presystolic venous pulse.

Positive Venous Pulse.—The positive venous pulse is the most important because of its diagnostic implications. It is the early, certain, and sometimes sole evidence of tricuspid insufficiency (Lancisi's sign). Moreover, it frequently permits the recognition without the ECG of the supraventricular or ventricular origin of extrasystoles and paroxysmal tachycardia. Its systolic timing (and not diastolic, as in the physiologic venous pulse) is the source of its frequent confusion with the carotid pulse, both being systolic in time and localized at the same site. Classical criteria to distinguish these two types consider that the positive venous pulse is visible but not palpable, and conversely, that the carotid pulse is better felt than seen (Cossio[5]), because the first is a volume pulse and the second a pressure pulse (Wiggers[5]). However, not rarely, and especially when a positive

venous pulse is due to ventricular tamponade, it is not only visible but is fairly palpable, lifting the palpating finger in some cases.

Another classical criterion is the presence or absence of liver pulsation (Dressler[7]). When it is present it definitely points to the venous origin of the cervical pulse; its absence, however, does not imply its carotid origin. Liver cirrhosis may have developed, as sooner or later happens in tricuspid insufficiency, and then no liver pulsation can be felt, in spite of the fact that a wide positive venous pulse is present in the neck. For these reasons the best criteria to distinguish the arterial or venous origin of cervical pulsations are shifts with respiration, manual abdominal pressure, and changes with decubitus. If with maneuvers no change in position is seen, the observed cervical pulsations are arterial. Their origin is venous if they shift headwards with expiration, manual abdominal pressure, or in the supine position—sometimes making the head pulsate (Musset's sign of venous origin) (Cossio[8]), and if they go caudalward with inspiration, cessation of abdominal pressure, or in the erect position.

But there is a simpler criterion that helps to distinguish the arterial or venous origin of palpable cervical pulsations. It is the phenomenon called discordance between the cervical and radial pulses. When wide pulsations are present in the neck and the radial pulse is small or barely palpable, they are always of venous origin. Obliterative arterial disease should be excluded by simultaneous bilateral palpation (Cossio[9]).

Clinical impression, checked with phlebography and with catheterization of the jugular veins in some cases, has allowed us to distinguish 3 types of positive venous pulse, each with individual characteristics and diagnostic implications that permit their recognition. They are: (1) the late systolic venous pulse, (2) the holosystolic, and (3) the early systolic venous pulse.

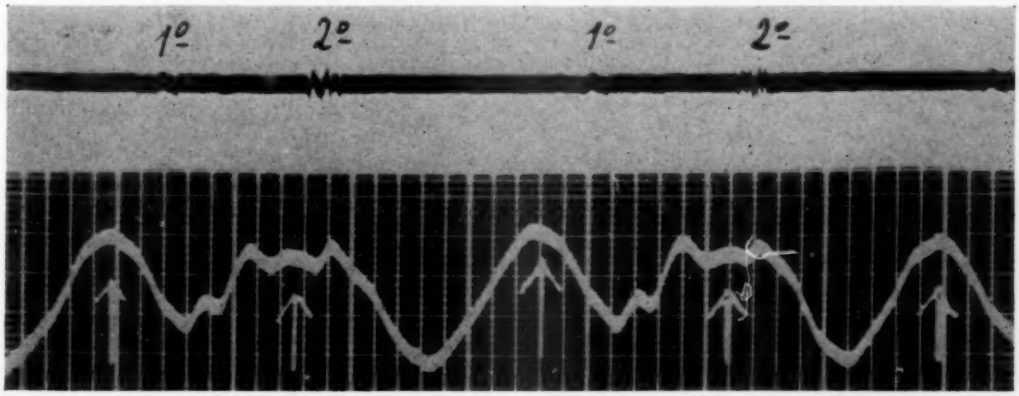


Fig. 3.—Late systolic positive venous pulse due to tricuspid regurgitation (undulating venous pulse).

Late Systolic Venous Pulse.—The late systolic venous pulse is an early and certain, and sometimes the sole evidence of functional or organic tricuspid insufficiency. In this type, the cervical systolic pulsation is coincident with the end of ventricular systole, due to the delay of the tricuspid reflux from the right atrium to the cervical veins. The delay is increased in proportion to the degree

of dilatation of the right atrium, superior vena cava, and jugular vein, to the distance between the right atrium and the neck, as well as to the systolic and diastolic pressure gradients existent in the right heart chambers.

This delay of the systolic wave results in its equidistance with the precedent and subsequent presystolic wave, the venous pulse showing a fairly typical configuration, the undulating venous pulse (Cossio[10]). With similar waves in time and amplitude, two for each cardiac cycle, a nonexperienced observer may wrongly diagnose an atrial flutter with 2:1 block, on this basis.

This characteristic appearence of the late systolic venous pulse is present especially in functional tricuspid insufficiency, because sinus rhythm is generally present and, therefore, the presystolic or *a* wave is clearly visible (Fig. 3).

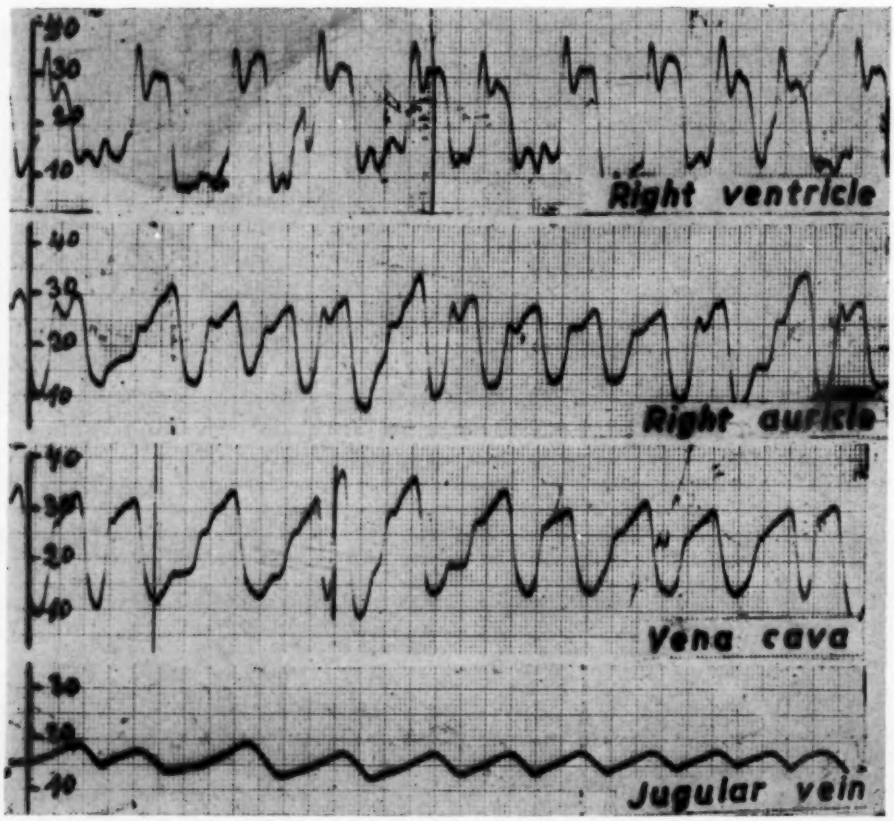
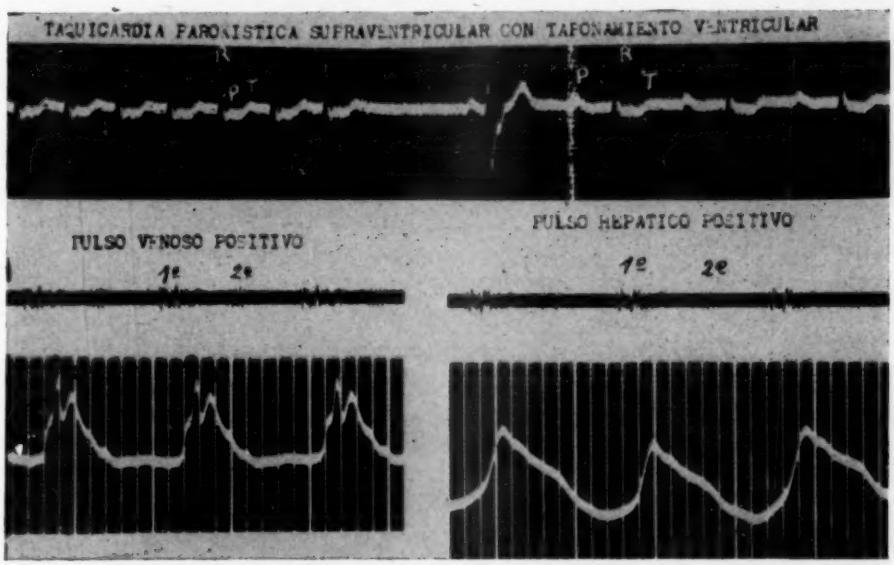


Fig. 4.—Late systolic positive venous pulse due to tricuspid regurgitation, as seen in the pressure tracings obtained during right heart catheterization.

In organic tricuspid regurgitation, on the other hand, auricular fibrillation is the rule, and the positive venous pulse is formed by the late (and single) systolic wave; this makes much more difficult its distinction from the carotid pulse and both may be easily confused. Changes with posture and the other mentioned characteristics should be used for diagnosis (Fig. 4).

Holosystolic Venous Pulse.—This is the other type of positive venous pulse of definite diagnostic value. It allows the recognition of the atrial or ventricular

origin of extrasystoles (Mackenzie[11] and Lewis[12]), and the ventricular or supraventricular type of paroxysmal tachycardia (Gallavardin,[13] Cossio[15]). It is due to the coincidence of atrial and ventricular systoles, the so-called ventricular tamponade (Wenckebach,[14] Moia[16]), with the resultant reflux wave to the venous system synchronous with ventricular systole. It is seen only in the lower part of the neck, as the venous valves are sufficient in the absence of chronic venous hypertension. It is due to this reason that it is generally rather palpable and varies little with changes in posture, respiration, or abdominal pressure. Its discordance with the radial pulse should be sought for its diagnosis. It is seen in ventricular (and not in auricular) extrasystoles, as well as in nodal and auricular paroxysmal tachycardia, in the latter only when atrial systole is coincident with the precedent ventricular systole, as happens in rapid cardiac rates or in prolonged P-R intervals. In ventricular paroxysmal tachycardia a systolic venous pulse may be seen only if auricular activity is present, as sometimes happens. In these cases its rate is lower than the arterial pulse (Gallavardin's sign) (Figs. 5, 6).



A. *B.*

Fig. 5.—*A*, Holosystolic positive venous pulse due to ventricular tamponade (supraventricular paroxysmal tachycardia); *B*, liver pulsation in the same patient.

Early Systolic Venous Pulse.—This last type of venous pulse is of academic rather than practical value. It is due to the sudden thrust from the aortic arch and its branches in the venous system and is produced by the unusually wide and strong pressure wave generated during ventricular systole, as happens in severe aortic insufficiency with marked diastolic reflux. For these reasons, the systolic venous pulse wave lasts only during, and is synchronous with, the first part of ventricular systole, being much more apparent on the left than on the right side of the neck because of the closer contact of the aortic arch with the innominate vein than with the superior vena cava and right jugular vein. "Arterial dance" is also present in the neck, as a rule; but changes with posture, respiration, and

abdominal pressure permit an estimation of the contribution of each one to the magnitude of cervical pulsations (Figs. 7, 8).

Absence of Venous Pulse or Fluttering in the Engorged External Jugular Vein.—The lack of venous pulse in a more or less engorged external jugular vein, in spite of respiratory movements and changes in posture, is due to the hemodynamic block of venous flow in superior vena caval obstruction (mediastinal syndrome), or to the lack of a mechanically efficient auricular activity, as happens in atrial fibrillation, although this latter and particularly atrial flutter can produce a weak but definitely visible fluttering in the superficial veins of the lower neck. Absence of pulsation in an engorged external jugular vein, slight or marked irregularity of the radial pulse, suggests atrial fibrillation, as well as an underlying cardiac condition in which it may be present, such as mitral stenosis, myocardial infarction, hyperthyroidism, etc.

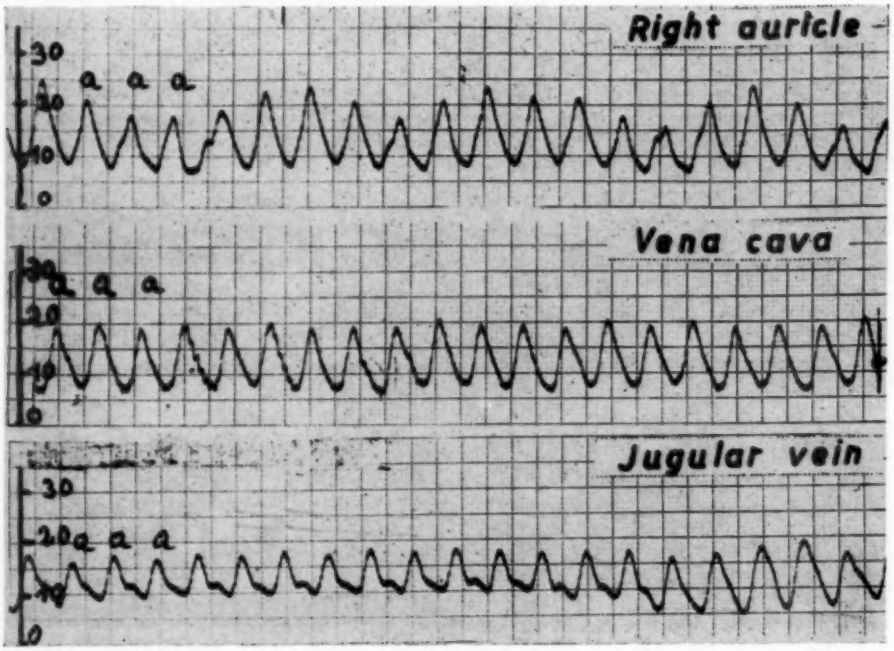


Fig. 6.—Holosystolic positive venous pulse, due to ventricular tamponade in supraventricular paroxysmal tachycardia, recorded during right heart catheterization.

Absence of Shifting of the Venous Pulse.—The lack of shifting of the venous pulse, which in this instance is usually small in spite of engorged jugular veins, is present in pericardial tamponade or chronic constrictive pericarditis. Moreover, this quality is useful in distinguishing the pericardial or pulmonary origin of pulsus paradoxus (mechanic versus dynamic pulsus paradoxus). In the first case, cervical veins are always engorged, and the venous pulse if present is seen in the same site without changes in amplitude. In the second type (dynamic pulsus paradoxus due to severe dyspnea with air passage obstruction, as happens in bronchial asthma), while the radial pulse may dissappear with each inspiration, the superficial cervical veins collapse and the venous pulse is exaggerated and displaced caudalward.

Giant Presystolic Venous Pulse.—This type of venous pulse shows only a presystolic wave of increased amplitude and duration because of the exaggeration of the normal *a* wave present in the physiologic venous pulse. This happens when atrial systole is longer and stronger than in normal conditions (tricuspid stenosis) or because right ventricular diastolic pressure is augmented (pulmonary stenosis, right ventricular failure, pulmonary hypertension). To integrate the clinical picture may help in the bedside recognition of the above-mentioned

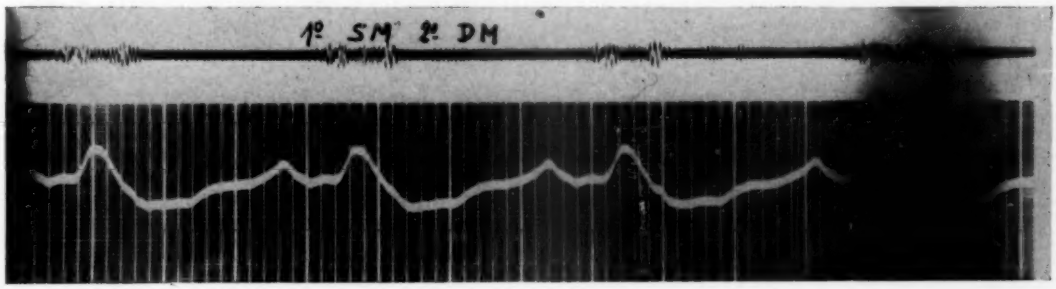


Fig. 7.—Positive early systolic venous pulse due to aortic regurgitation.

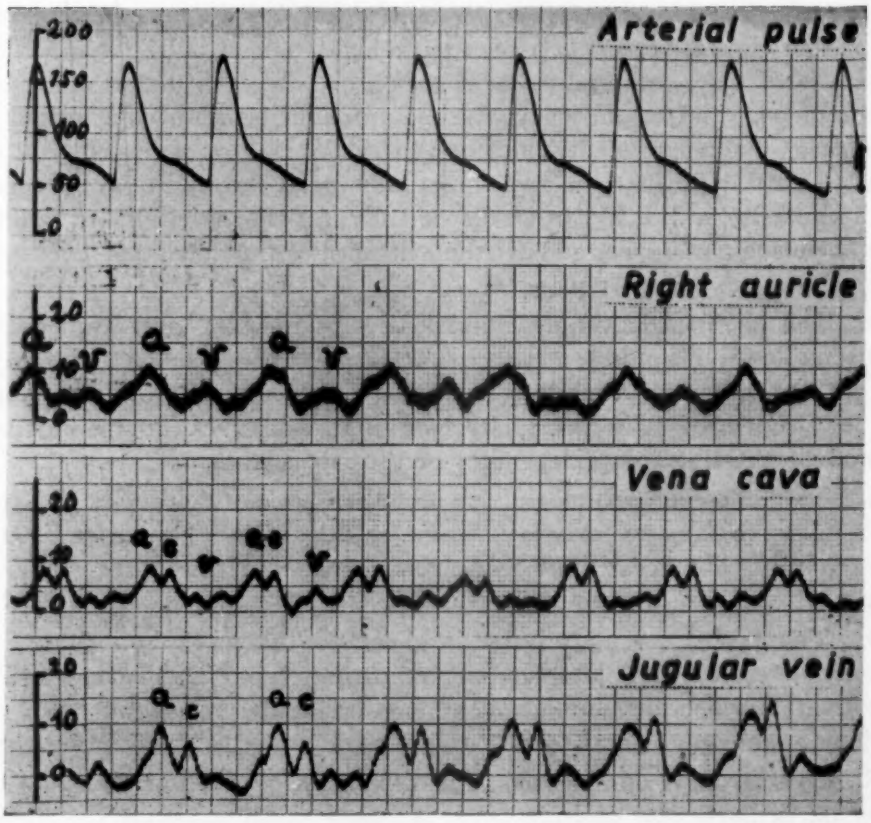


Fig. 8.—Positive early systolic venous pulse due to aortic regurgitation recorded during heart catheterization. Femoral arterial pressure 175/50 mm. Hg.

conditions; it is not rarely confused with the systolic venous pulse of functional tricuspid insufficiency in the presence of right heart failure. The motion to-and-fro between arterial and venous pulsations and the coincidence of the *a* wave with the first heart sound indicate the presystolic nature of the venous pulse (Fig. 9).

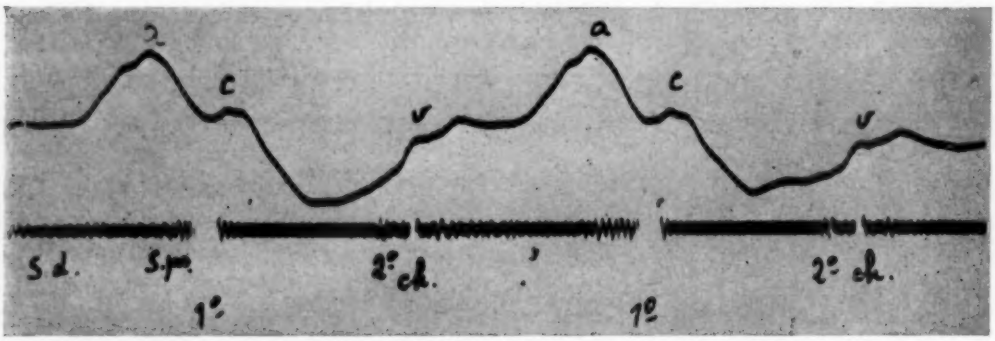


Fig. 9.—Giant presystolic venous pulse in a patient with mitral stenosis and pulmonary hypertension. The typical auscultatory features can also be seen in the simultaneously recorded phonocardiogram.

SUMMARY AND CONCLUSIONS

1. The clinical recognition of a pathologic venous pulse by inspection of the neck is of diagnostic value, as it makes possible the diagnosis of (a) the presence of tricuspid insufficiency, (b) the auricular or ventricular origin of extrasystoles, (c) the supraventricular or ventricular nature of paroxysmal tachycardia, (d) atrial fibrillation, and sometimes atrial flutter, in the presence of pulse irregularity and tachycardia, respectively, (e) the pericardial or pulmonary origin of pulsus paradoxus, and (f) the existence of pulmonary or tricuspid stenosis, or pulmonary hypertension.

2. The physiologic venous pulse is always diastolic and formed by two waves (double venous pulse), usually a smaller one (*v* wave) followed immediately by a greater (*a* wave). For this reason it is named ascending two-step-stair type; less frequently it is formed by two separated waves (double independent type waves), the appearence depending on the cardiac rate.

3. The following pathologic venous pulses are distinguished: (a) positive venous pulse, (b) absence of venous pulse or fluttering in an engorged external jugular vein, (c) absence of shift of the venous pulse, (d) giant presystolic venous pulse.

4. The positive venous pulse is clinically the more important. Three types are described: (a) late systolic, due to tricuspid insufficiency, with one distinctive subtype, the undulating venous pulse, (b) the holosystolic, due to ventricular tamponade, and (c) the early systolic, due to aortic insufficiency.

5. It is strongly emphasized that distinction between arterial and venous pulses, particularly the positive type, is based much more on the distinctive qualities of shift, configuration, and discordance than on the classical criteria of timing and palpability.

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CATHETERIZATION OF THE CORONARY ARTERIES OF INTACT DOG

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DURING a routine catheterization of the pulmonary vein, it was noted that the catheter shadow was running along the wall of the left ventricle. It appeared that the catheter had penetrated the pericardial sac, but an autopsy revealed the catheter to be tightly wedged into the left anterior descending coronary artery. Although attempts to duplicate this procedure were made repeatedly, it was not until recently that it was possible to perform this catheterization with any positive anticipation of success. At the present time, catheterization of a coronary artery has been accomplished in approximately three of every four trials. In this report some of the normal data obtained is being presented in addition to some preliminary information from experiments now being performed.

METHOD

Twelve dogs having an average body weight of 21 Kg. were used in 13 experiments. They were given 30 mg. per kilogram of Nembutal intravenously. During the next hour the various catheters were placed in the proper vessels and catheterizations were conducted under fluoroscopic guidance. When vascular pressures were being obtained, the animals received 5 mg. per kilogram of heparin intravenously. On different occasions catheters were positioned in coronary sinus, right atrium, right ventricle, pulmonary artery, left ventricle, and pulmonary vein. Usually the coronary sinus and left ventricle were catheterized in addition to the coronary artery. A small branch of the femoral artery was cannulated for recording of arterial pressure. The coronary arteries were catheterized with either a 7.5 to 9 F. or a 5.5 to 7 F. bird's-eye-tipped catheter 75 cm. in length. The catheter had no bend at its tip. It was passed down either the right or left carotid artery and on entering the ascending aorta it was carefully kept close to the left lateral surface of this vessel. As the catheter touched the semilunar valves it was retracted slightly and the tip turned toward the ventral surface of the animal. The catheter generally entered the left anterior descending coronary artery. The right coronary artery was not readily accessible to catheterization and the two successful penetrations may well be considered as being accidental. Some of these catheters were fitted to record electrocardiograms. No difference in ease of catheterization was noted with

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either catheter. When double-lumen catheters were utilized to enter the coronaries, the other lumen was available for recording of aortic pressures. Limb electrocardiographic leads were taken in addition to those obtained from the cavities of the heart and the coronary artery. All recordings were made on Sanborn Twin Visos with appropriate amplifiers and transducers. Pressures and electrocardiograms were taken continuously during the experiment. The pressures were all referred to the right atrium as the point of zero reference.

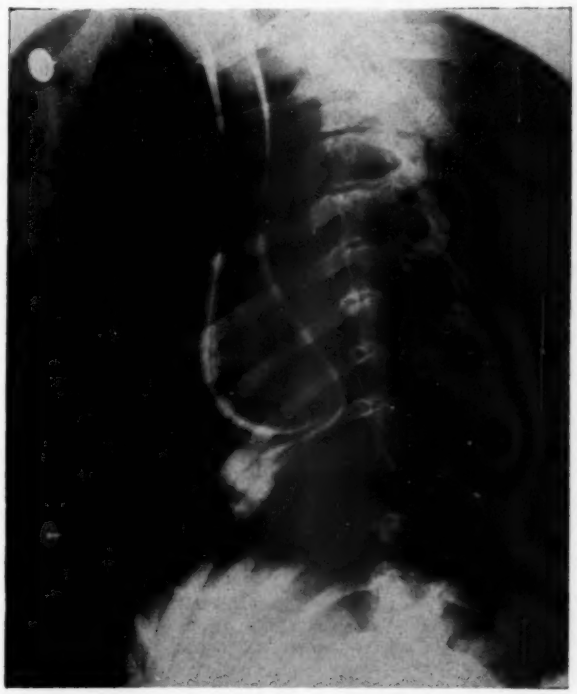

Fig. 1.—Catheters found in coronary sinus and left anterior descending coronary artery. Diodrast had been injected into the coronary artery catheter and the extent of the arterial bed beyond the catheter demonstrated.

The coronary catheter was advanced as far down as possible for the purpose of obtaining a "wedged pressure." The first 8 animals were deliberately sacrificed at the termination of the experiments and the positions of the catheters were determined. Measurements of the depth of penetration down the arterial tree were made. Utilizing this information, it was possible to estimate the depth of penetration to within 5 mm. on those animals not immediately sacrificed. Injections of cold saline, epinephrine, acetylcholine, and other drugs were made into the coronary artery and, at other times during the experiment, into various other vessels or cardiac cavities for purposes of comparing patterns and degrees of response. Those dogs on whom survival from the procedure was being determined had the catheters removed, their incisions sutured, and received 300,000 units of procaine penicillin intramuscularly. One animal was again catheterized after a two-month period of recuperation. He exhibited no evidence of abnormal cardiac function, 2½ months after the second catheterization.

TABLE I. CATHETERIZATION OF CORONARY ARTERIES

EXPERIMENT NUMBER	SITE	DISTANCE (MM.)	DURATION (MIN.)	SURVIVAL
1	L.A.D.	60	100	Sacrificed
2	L.A.D.	83	60	Sacrificed
3	L.A.D.	38	156	Sacrificed
4	L.A.D.	50	203	Sacrificed
5	R.C.	70	163	Sacrificed
6	L.A.D.	38* and 100*	135	Sacrificed
7	L. Cir.	25	128	Sacrificed
8	R.C.	78	130	Sacrificed
9	L.A.D.	90	151	Survived
10	L.A.D.	38*	160	Dead 48 hrs.†
11	L. Cir.	63	35	Ventricular fibrillation
12	L. Cir.	78*	195	Survived
12a	L.A.D.	100*	170	Survived

L.A.D. = Left Anterior Descending; R.C. = Right Coronary; L. Cir. = Left Circumflex.
Experiment 12a was performed two months later on the animal used for experiment 12.
*Estimated by measurements during fluoroscopy.
†Infarcts on right ventricular wall.

TABLE II. ARTERIAL PRESSURES AND HEART RATES THIRTY MINUTES AFTER CATHETERIZATION OF THE CORONARY ARTERY

EXPERIMENT NUMBER	ARTERIAL PRESSURE (MM. Hg)			CORONARY ARTERY PRESSURE (MM. Hg)			HEART RATE PER MINUTE
	SYSTOLIC	DIASTOLIC	MEAN	SYSTOLIC	DIASTOLIC	MEAN	
2*	—	—	110	48	18	28	150
3*	120	105	110	48	18	28	150
5*	120	105	110	36	28	31	160
8*	133	80	98	29	16	22	108
10*	125	95	105	30	25	27	162
11*	—	—	—	33	24	27	
12*	190	110	137	48	28	35	96
12a*	140	70	94	50	17	28	66
Mean*	138	94	109	40	22	28	127
4	125	95	105	70	50	57	160
6	—	—	—	94	79	84	147
7	136	116	123	85	62	70	108
1†	190	108	136	151	137	142	132
3†	160	118	132	120	105	110	160
6†	145	125	130	132	118	123	192
9†	160	120	133	141	118	126	132
10†	135	108	117	125	113	117	180
Mean†	158	116	130	134	118	124	159

*The coronary artery pressures were "wedged pressures."

†Coronary artery pressures within 2 to 5 cm. from ostium. In animals 4, 6, and 7, the catheter was found to partially occlude a major branch of the coronary artery.

RESULTS AND DISCUSSION

The data pertinent to this report are summarized in Tables I and II. The position of the catheter in the left anterior descending coronary artery is shown in Fig. 1. Diodrast was injected and the amount of cardiac tissue being supplied beyond the tip of the catheter was readily visualized. In some instances the catheter tip was at the very lowest part of the apex of the heart and a very small quantity of cardiac muscle could be observed and be said to be supplied by coronary blood. The data in Table I indicate the length of catheter in the coronary arteries, measured from the opening of the arteries in the aorta. Except for one instance where fibrillation intervened, the catheters were left in place for periods from 1 to over 3 hours. In some of these experiments the catheter was "wedged" for the entire period of observation.

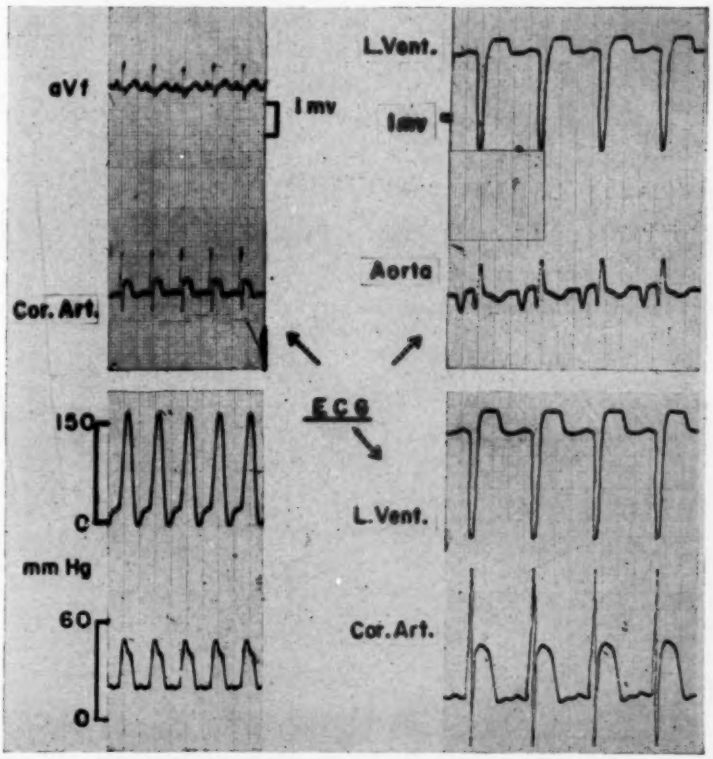

Fig. 2.—Some electrocardiographic tracings obtained during catheterization of the coronary artery. In this animal catheters with electrocardiographic leads were placed in the left ventricle and 38 mm. down the left anterior descending coronary artery and occluding a small branch.

The successful catheterization of the first 8 animals was purely of academic interest. In order to determine the ultimate usefulness of the procedure, the next 4 animals, after being catheterized, had the catheters removed, their wounds sutured, and then were returned to their cages for further observations. Two of these dogs survived the procedure successfully. No evidence of permanent damage was noted in the electrocardiographic tracings taken during the next few months. A second successful catheterization was accomplished in 1 of

these dogs 2 months later. The third animal fibrillated during the experiment and the last animal (Fig. 4) died 2 days later. The presence of infarcts on the right ventricular wall of this dog was not accounted for readily.

The electrocardiographic tracings obtained from the coronary artery are similar to those obtained from epicardial leads (Fig. 2). The vascular pressure relationships between left ventricle and coronary artery are also shown in this illustration. Coronary artery and femoral artery pressures are summarized

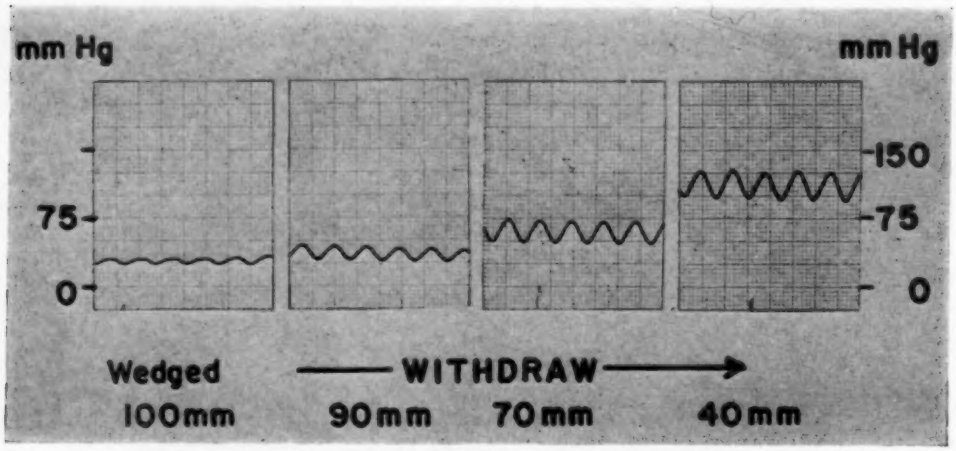

Fig. 3.—Pressures obtained during the withdrawal of a catheter from its wedged position in the left anterior descending coronary artery.

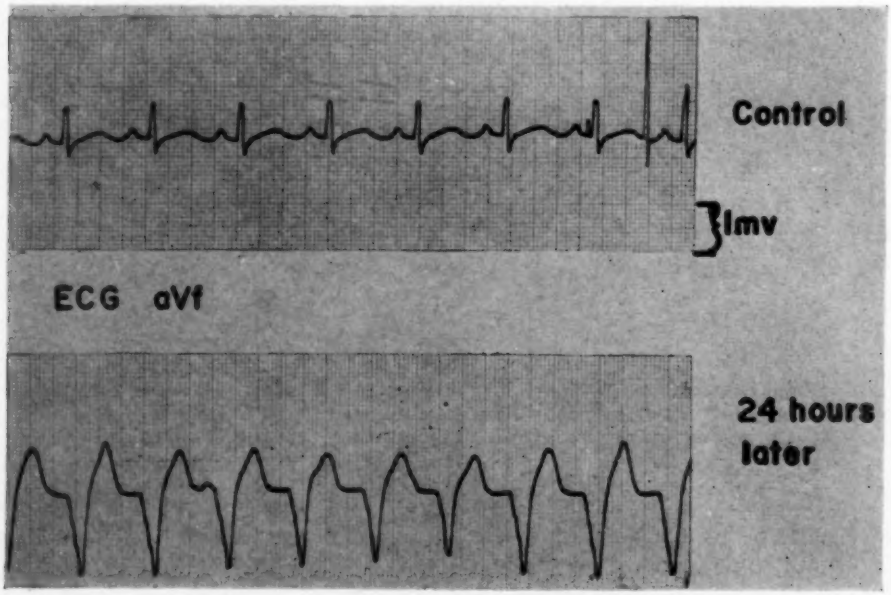

Fig. 4.—Augmented limb lead obtained from Dog 9 just before he was returned to his cage following catheterization (control) and again 24 hours later. An occasional ectopic beat was noted following the removal of the coronary artery catheter. Autopsy revealed several large and small infarcts on the epicardial surface of the right ventricle.

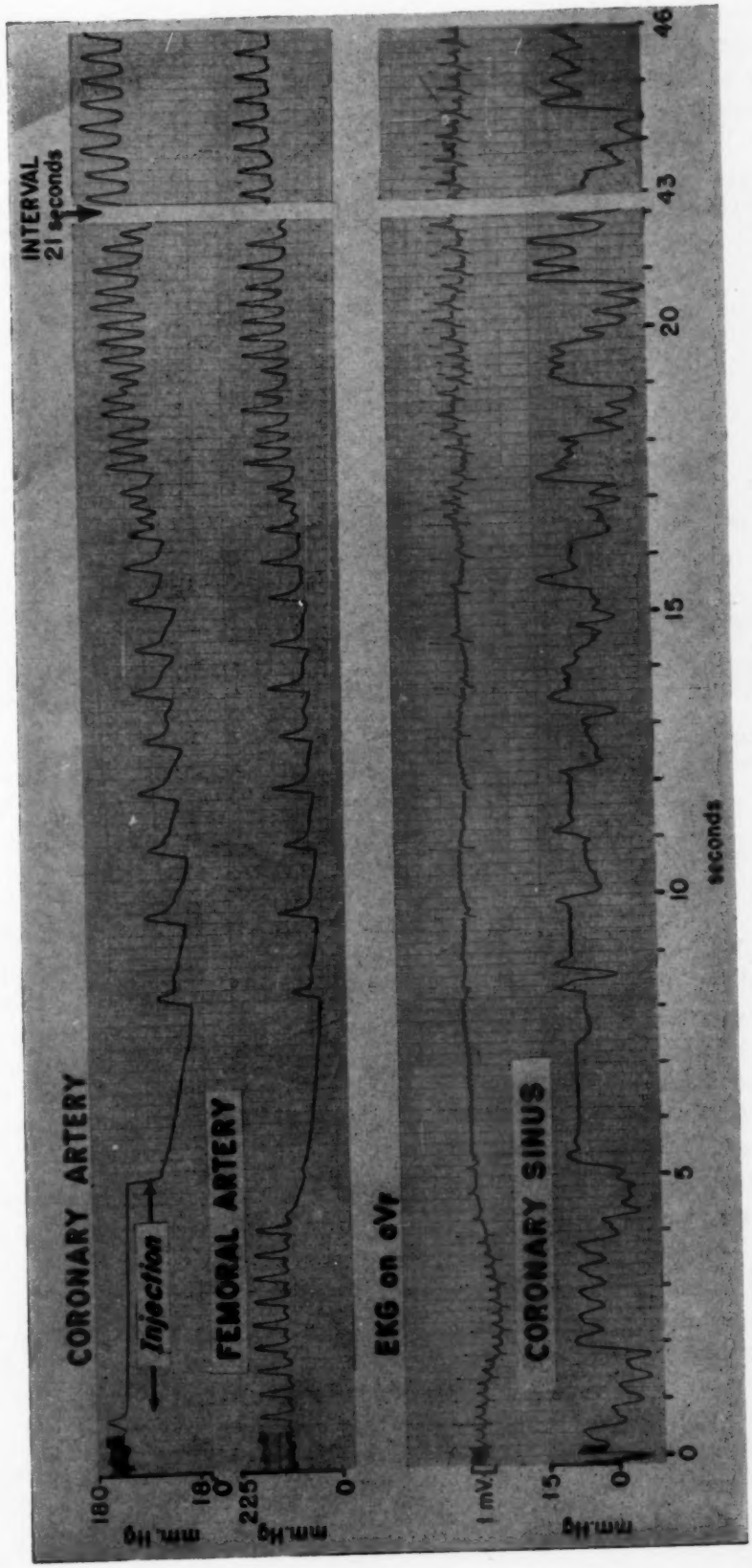

Fig. 5.—The effects of injection of 40 μg. of acetylcholine chloride into the coronary artery. The catheter was approximately 90 mm. down the left anterior descending coronary artery. This animal is still living.

in Table II. The "wedged" coronary artery pressure may represent the pressures observed in the arteriolar portion of myocardial capillaries. The values obtained are at least suggestive in that they agree with those reported by Landis[1] for the same site in peripheral capillaries.

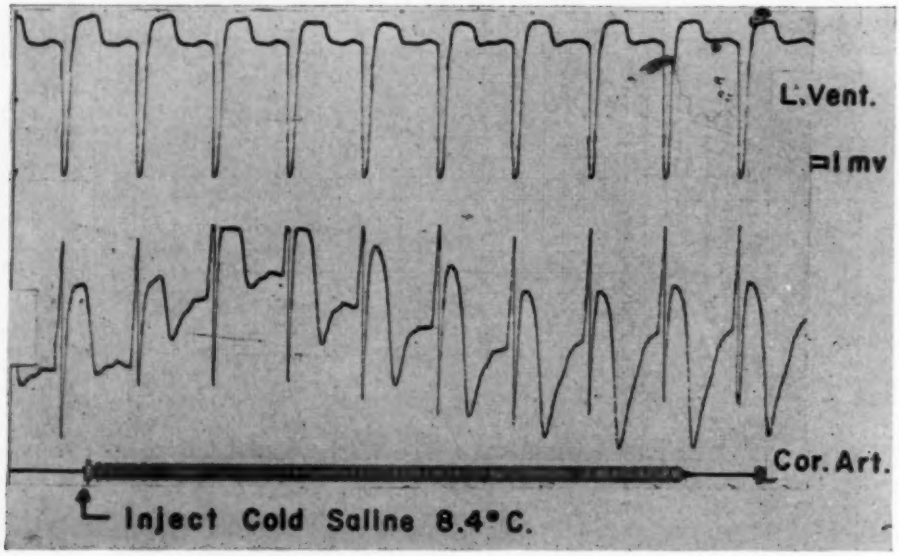

Fig. 6.—The influence of cold on electrocardiograms obtained from the left ventricular cavity and the coronary artery. Five milliliters of cold saline were rapidly injected into the left anterior descending coronary artery.

The coronary artery pressures recorded when the catheter was apparently lying free in the vessel are slightly lower than those occurring in the femoral artery. The 6 mm. lower mean pressure in the coronaries were a consequence of the hydrodynamics of the system representing in part the velocity component which was subtracted from the total pressure. Consequently, it could be inferred that the pressures in the two arterial beds were the same and that the catheter did not greatly interfere with the free flow of blood into the cardiac musculature. The failure to observe any marked alterations in the electrocardiogram during the procedure also indicated that the myocardium was not being subjected to any great degree of anoxia.

Fig. 3 illustrates the change in pressure in a coronary artery as the catheter was withdrawn from its wedged position to a point where it was lying free in the artery. The femoral arterial pressure in this animal was 130 systolic, 100 diastolic, and 113 mm. Hg mean.

The potentialities for direct catheterization of the coronary artery in intact animals as an investigative tool are illustrated by the data presented in Figs. 5 and 6. Other possibilities are readily evident. The direct injection of drugs and other chemical agents into a precise portion of the myocardium and a comparison of the hemodynamic responses to such an injection with injections elsewhere in the vascular system could provide valuable information. In Fig. 5

the injection of a relatively large amount of acetylcholine chloride, 40 μg., into the artery while a number of other phenomena were being measured illustrates the potentialities of such correlative studies. Data obtained from experiments similar to this will be reported in future publications. Similarly, the direct recording of electrocardiograms from specific areas of the myocardium of intact animals can prove to be a valuable tool to further studies on the genesis of electrical activity and propagation of impulse in normal and pathologic hearts (Fig. 6).

This demonstration of the feasibility of catheterizing the coronary artery of the intact animal makes available another approach to the study of cardiac dynamics. Although this procedure has been accomplished without inducing any untoward effects in some experimental animals, it is not always innocuous. Further evaluation of this technique is necessary. Experimental work in progress utilizing this method of coronary artery catheterization will be reported in detail later.

SUMMARY

Catheterization of the coronary arteries in the intact animal has been successfully accomplished in 12 animals. "Wedged" pressures have values similar to those observed in the arteriolar end of peripheral capillaries. "Free" pressures in the coronary artery are essentially the same as in the larger arteries. Catheters have remained in these vessels for periods exceeding 3 hours without producing evidence of injury. It is not, however, a procedure without danger. Potential applications of this technique to further understanding of cardiac dynamics have been illustrated by preliminary data from experimental work now in progress.

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Clinical Reports

PERICARDITIS COMPLICATING MYOCARDIAL INFARCTION

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DRESSLER[1] recently described a syndrome following a myocardial infarction consisting of prolonged fever, chest pain, involvement of the pericardium, pleura, or pulmonary parenchyma. Frequent relapses occurred, but the prognosis in all was favorable.

It is not uncommon during the second to fourth day, or even a few days later in the course of the myocardial infarction, to observe a pericardial friction rub lasting a few hours to a few days. This has been considered as the extension of the inflammatory process from the underlying muscle to the pericardial layer.[2]

CASE REPORTS

CASE 1.—L. B., a 59-year-old, white male schoolteacher, complained for the first time of severe back pain with radiation to the anterior chest on Oct. 16, 1955. This lasted all day and was accompanied by a cold sweat, chilliness, and weakness. The past history was noncontributory. He never had rheumatic fever, hypertension, or diabetes. He gave no allergic history, nor was there such history in any member of his family. On the initial examination, he appeared anxious, but was not acutely ill. Blood pressure was 160/100 mm. Hg. The heart was not enlarged; the sounds fair, $A_2 = P_2$; rhythm was regular. Neither a gallop nor a friction rub were audible. There were no signs of decompensation. The electrocardiogram (Fig. 1) was typical of a posterolateral wall myocardial infarction.

Course: On the third day (Oct. 18, 1955), the temperature rose to 101.4° F., yet the patient was more comfortable, the chest and back pain having subsided. On the following day (October 19), he experienced some chest pain on deep breathing. This lasted for about 48 hours. He then felt well until October 30 (the fifteenth day of illness), when he mentioned that a deep breath "brought a sensation of something in my chest."

The examination on October 18, revealed the presence of a friction rub audible over his entire precordium. This persisted until November 7 (20 days). On October 20, râles and bronchial breathing were heard at the bases. These subsided after a few days. The temperature (Fig. 2) continued hovering over 100° F. until October 31 (sixteenth day of illness), when it rose to 101.1° F. That night the patient was uncomfortable, especially when breathing deeply, and was quite apprehensive. Dullness on percussion was evident over the entire length of the

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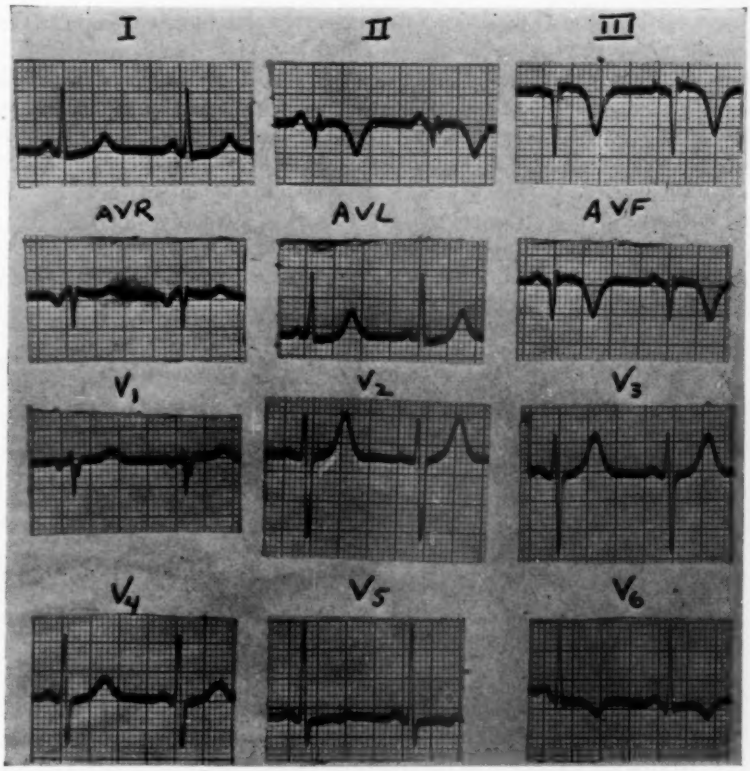

Fig. 1.—Case 1. Posterolateral wall myocardial infarction.

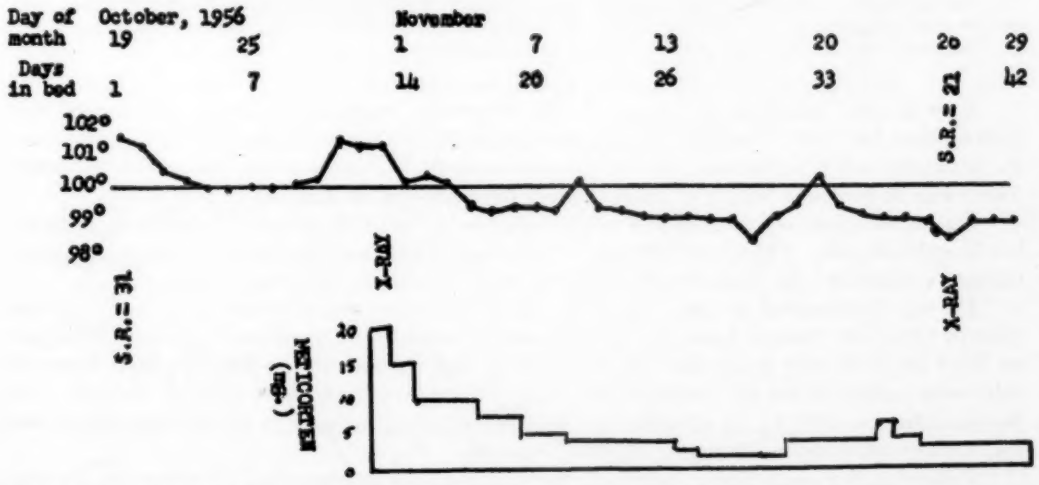

Fig. 2.—Case 1. Note irregular though prolonged period of fever and dosage of Meticorten required to maintain an afebrile state.

sternum. X-rays of the chest (Fig. 3) revealed marked enlargement of the cardiac silhouette, consistent with the presence of a pericardial effusion.

On October 31, the patient was placed on Meticorten, 10 mg. 4 times daily. Within 24 hours he felt quite comfortable and the steroid medication was continued, but in decreasing doses. The temperature fell promptly and was normal on November 4 (nineteenth day of illness), and remained there. Aside from occasional heaviness in the chest, unrelated to exertion, he has felt well. He returned to work on Dec. 1, 1955, still taking Meticorten 2.5 mg. twice daily. A repeat chest roentgenogram on November 26 (Fig. 4) revealed a normal cardiac silhouette.

On October 19, the white blood count was 10,600, segmented 79, stabs 3, lymphocytes 17. The sedimentation rate was 30 mm. in 1 hour; on November 26, the sedimentation rate was 21 mm. in 1 hour.

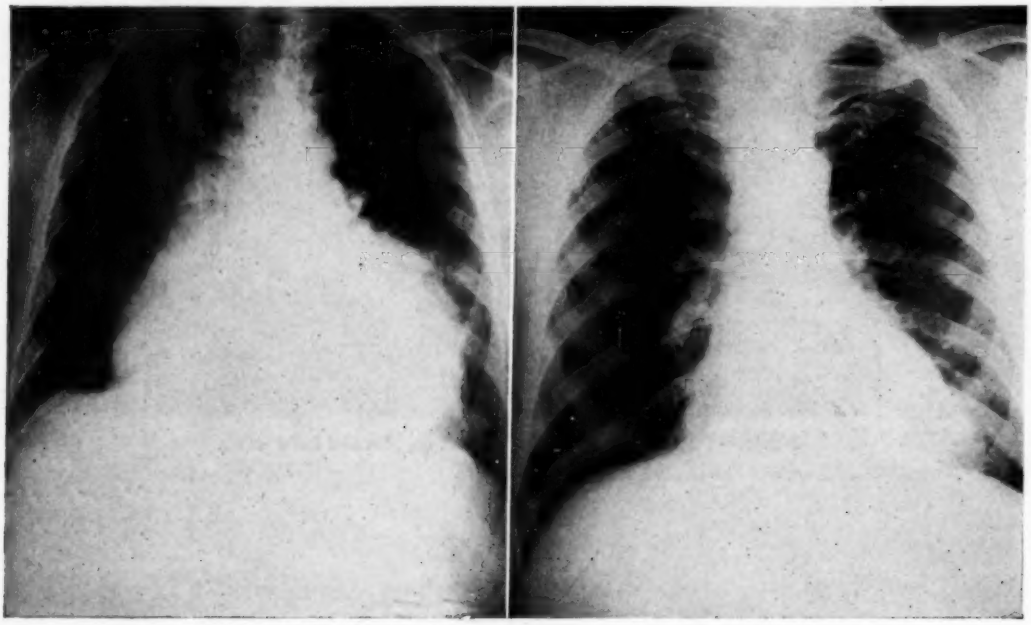

Fig. 3. *Fig. 4.*

Fig. 3.—Case 1. Oct. 31, 1955. Cardiac silhouette indicative of a large pericardial effusion and congestive lung changes.

Fig. 4.—Case 1. Nov. 26, 1955. Normal cardiac silhouette.

CASE 2.—M. S., a 52-year-old, white male stagehand, complained of chest pain for the first time on May 19, 1955. The pain was located substernally with no radiation and was accompanied by weakness and perspiration. It was present more or less continuously for about 36 hours. There was no previous history of heart disease, hypertension, or diabetes.

On examination, the patient was acutely ill, perspiring freely, without cyanosis or dyspnea, but in evident pain. Otherwise, there were no unusual findings. An electrocardiogram showed changes consistent with an early posterolateral wall myocardial infarction (Fig. 5).

He was hospitalized on May 21, 1955, placed in an oxygen tent and given anticoagulant therapy (May 21 through June 21) and adequate sedation. He complained again of chest pain on May 26, 1955 (one week after the onset of his illness), and on the following day numerous râles were audible in the left posterior chest from the angle of the scapula down to the base. The temperature was 102° F. A portable film showed an area of density in the left lower lung field and a diagnosis of probable pneumonia was ventured.

Following the institution of antibiotic therapy, the lung findings slowly receded and the temperature declined. On June 6 (18 days after onset), the portable chest x-ray revealed a small area of residual density in the left lower lobe and a diagnosis was made of a resolving pneumonia.

On this morning, the patient complained again of substernal pressing pain. A rapid heart rate was noted and an electrocardiogram indicated a ventricular tachycardia. Quinidine sulfate and later Pronestyl medication was administered with restitution of sinus rhythm on June 9, 1955.

From then on his hospital course was uneventful. He never had calf tenderness nor gross hemoptysis. Homans' sign was always negative. There were no symptoms with ambulation. On June 24, chest roentgenograms revealed horizontal streaklike densities in the left lower lung

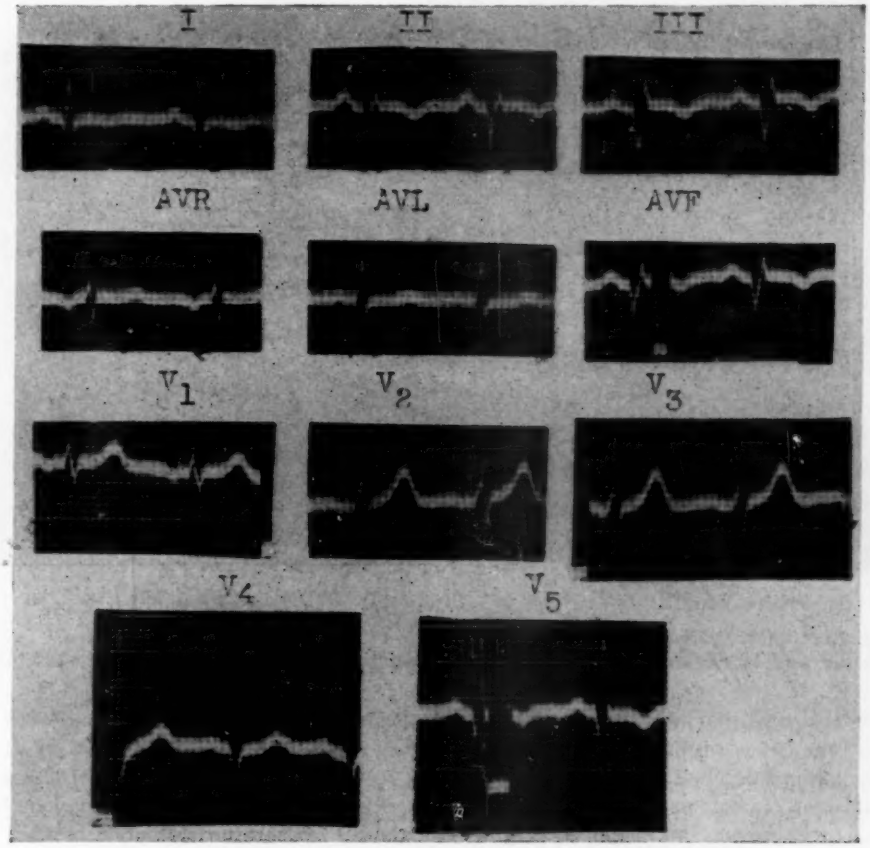

Fig. 5.—Case 2. Myocardial infarction involving the posterior and lateral walls.

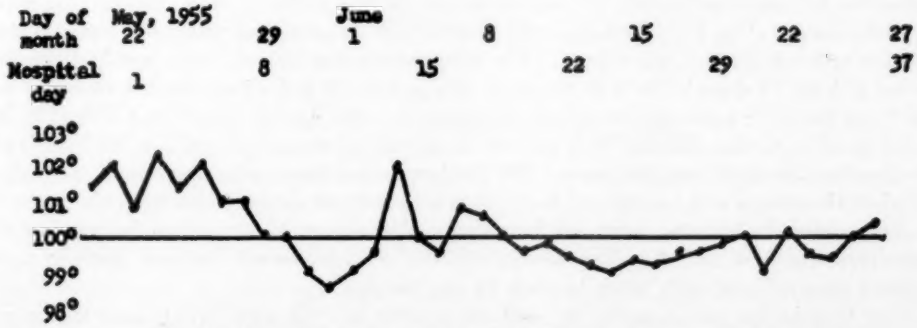

Fig. 6.—Case 2. Note persistence of low-grade fever even on discharge from hospital.

field which the interpreter thought could be due to platelike atelectasis, pulmonary infarction, or residual pneumonitis.

Laboratory studies including urines and blood chemistries were normal. On May 21, the white blood cell count was 28,550; on May 26, 14,000. On May 24, the sedimentation rate was 20; on May 25, 28; on June 1, 10.

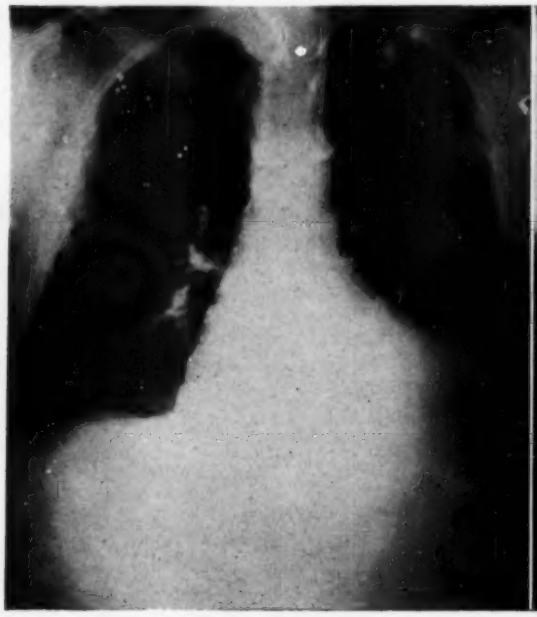

Fig. 7.

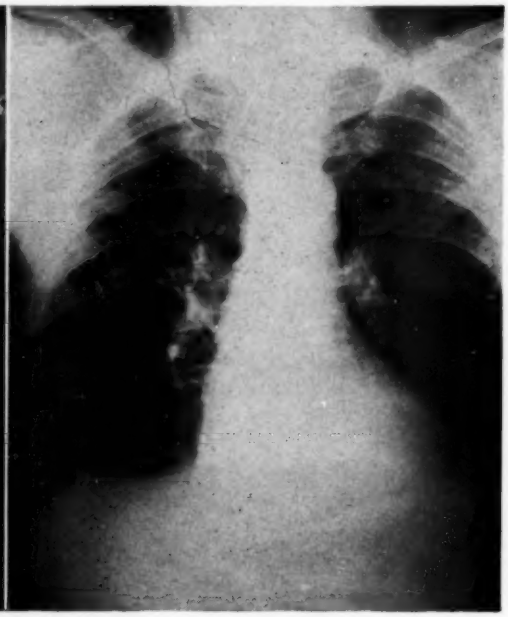

Fig. 8.

Fig. 7.—Case 2. Cardiac shadow enlarged Oct. 5, 1955.
Fig. 8.—Case 2. Later normal, Oct. 29, 1955 (indicative of disappearance of pericardial fluid).

The temperature chart (Fig. 6) showed only short intervals of normality, and even on discharge (June 27) when he was symptom-free, he still had some fever—100.4° F.

The patient felt well at home until about July 28, 1955 (9 weeks after onset of illness), when he complained of chest pain radiating to the back and abdomen and lasting for a period of 5 days. Unfortunately, he was not examined at that time and his temperature was not taken.

On Sept. 17, 1955, about 7 weeks later (16 weeks after onset of myocardial infarction), he began to cough, and ran a fever up to 104° F.; numerous medium râles were present at the left base. He was treated with antibiotics and after a week felt better, although not well. His temperature continued between 100° and 101° F. On October 5, he noted pain in his anterior chest, radiating to his back and to the right. The pain was worse on breathing and lying down. On examination he appeared acutely ill and distressed on lying down. The cardiac silhouette on x-ray was enlarged (Fig. 7). The lungs were clear except for streaking at the left base. The sedimentation rate was 20 mm. per 1 hour. The temperature was 101° F. (He had had continuous fever for at least 19 days.) He was placed on Meticorten 10 mg. t.i.d. Within 24 hours he felt like a "new person"; pain and fever had disappeared. On October 29, a chest film (Fig. 8) revealed a smaller cardiac shadow (this pointed to the disappearance of pericardial fluid) and the sedimentation rate was 6 mm. per hour. The Meticorten had been reduced gradually until Nov. 1, 1955, when the dosage was 2.5 mg. per day. At this time there was recurrence of pain in the chest, back, and under the left ribs, worse on breathing. The patient had to sit up for comfort. The temperature was now 101° F. The Meticorten was then increased stepwise and the patient's symptoms were relieved only when he took 20 mg. per day.

Since then he has continued to feel well and is afebrile. His exercise tolerance was increased so that he was able to return to part-time employment by Dec. 30, 1955. The steroid medication had been gradually reduced until Dec. 18, 1955, when it was discontinued.

DISCUSSION

The syndrome which these patients illustrate involves disease of the pericardium, the pulmonary parenchyma, and possibly the pleura. It resembles in this respect the so-called benign idiopathic pericarditis and the postcommissurotomy syndrome[3] except that it appears following a myocardial infarction. Like these conditions, it is also prone to recurrences, the reason for which is unknown. This condition may be readily overlooked as one does not usually subject a patient with an acute myocardial infarction to teleoroentgenograms of the chest. On the other hand, if a single x-ray study shows enlargement of the cardiac silhouette, one is usually satisfied to make a diagnosis of enlargement of the heart. Serial x-rays are required to extablish the diagnosis of effusion within the pericardium. The changing size of the cardiac silhouette indicated the presence of pericardial fluid.

The presence in these patients of a pulmonary infarction seems unlikely, although it is recognized that emboli to this organ need not give any symptoms or signs. There was no gross hemoptysis nor calf tenderness at any time. Pericardial effusion is not expected as an accompaniment of lung infarction. A diagnosis of extension of the myocardial infarction might be ventured, but there was no evidence to substantiate this impression.

The incidence of pericarditis in myocardial infarction differs widely with various authors. In post-mortem material, Langendorf[5] found in 15.3 per cent diffuse involvement of the pericardium. Stewart and Turner[4] state that 25 to 32 per cent of patients with myocardial infarction have some localized pericardial involvement. Pericardial effusion has been considered unusual, if not rare.[2,6]

CONCLUSION AND SUMMARY

Two patients have been described with recurrent chest pain, fever, and evidence of pericardial fluid for a prolonged period following an acute myocardial infarction. This complication of pericarditis following a myocardial infarction resembles nonspecific pericarditis and the postcommissurotomy syndrome. Its benign character and its confusion with pulmonary embolization and extension of myocardial infarction have been mentioned. One should be alerted to this possibility when either the fever, the chest pain, or pericardial friction rub endures longer than one expects them to in an individual with a myocardial infarction.

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ADDENDUM

Case 1.—On Jan. 21, 1957, the patient suffered with a recurrence of anterior chest pain on breathing, which condition lasted a week. This rapidly subsided with Meticorten, 10 mg. three times a day.

REDUCTION OF CARDIAC OUTPUT BY LIGATION OF THE INFERIOR VENA CAVA IN PATIENTS WITH ATRIAL SEPTAL DEFECTS COMPLICATED BY PULMONARY HYPERTENSION

(A Report of 2 Cases)

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INTRODUCTION

Ligation of the inferior vena cava below the renal veins has been reported to prevent recurrences of pulmonary embolism[1,2] and to relieve intractable heart failure in patients with various types of heart disease, including atrial septal defects.[3-5] Since the hemodynamic effects were not determined, it is our purpose to report the changes observed in 2 patients with atrial septal defect complicated by venoarterial shunting due to pulmonary hypertension which precluded surgical closure of the defect.

METHOD

The usual clinical methods of evaluation were employed. Exercise tolerance was evaluated in terms of responses to walking on a treadmill on a 10 per cent grade at 1.7 mph for 10 minutes.[6] Blood volumes were evaluated by either T-1824 or I^{131} labeling of plasma; venous hematocrits were corrected for plasma trapping. Venous catheterization of the heart was done on 3 occasions in each patient.

CASE REPORTS

Case 1, E. I. (KCH 214676), experienced no physical limitation until the age of 37 years, when cough, chest pain, loss of weight, and exertional dyspnea first occurred.

By age 40 years, hemoptysis and cyanosis had developed. Atrial septal defect was demonstrated anatomically during cardiac catheterization. Two years later cardiac catheterization revealed pulmonary pressure to be 75/40 mm. Hg. Peripheral arterial O_2 saturation was 84 per cent. Heart failure progressed despite treatment.

An attempt to relieve chronic venous hypertension with pentolinium (240 mg. every 8 hours) reduced circulation time and venous pressure without producing any subjective improvement. Subsequently, ligation of the inferior vena cava below the renal veins was performed on April 14, 1955.

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*Trainee of the National Heart Institute, 1955-1956.

Venous pressure in the arms decreased from 22 to 8 cm. of saline, and by the eleventh postoperative day, dyspnea on ward activity, nocturnal cough, and orthopnea had regressed. Vital capacity increased from 1.3 to 2.0 L., and maximum breathing capacity from 26 to 34 L. per minute. The arterial O_2 saturation increased to 95 per cent. Exercise tolerance improved slightly with an increase in the physical fitness index from 1.2 to 2.1. Another catheterization of the heart showed diminished blood flows and decreased right ventricular pressure (Table I).

After this transient improvement, his status again deteriorated and he was hospitalized for the last time on Oct. 26, 1955. Despite vigorous treatment for congestive heart failure, he expired on Oct. 31, 1955, at the age of 44 years.

At post-mortem examination, edema of the legs and lungs, ascitic fluid, and hepatomegalia were present. The heart weighed 920 grams and was markedly dilated and hypertrophied. The right ventricular wall measured 3 to 6 mm., and the left ventricular wall measured 13 mm. The

TABLE I. HEMODYNAMIC OBSERVATIONS AT REST

PATIENTS	E.I.		H.H.	
Relationship to Caval Ligation	Preop. 12/3/53	Postop. 6/8/55	Preop. 4/11/55	Postop. 11/7/55
Hematocrit, %	51	46	50	46
Hemoglobin, gm. %	13.8	13.2	18.2	14.3
Oxygen consumption, ml./min.	225	210	265	285
O_2 Saturation, %				
Caval (C)	65	50	74	49
Right Atrium (RA)	72	61	83	67
Right Ventricle (RV)	75	61	82	70
Pulmonary Artery (PA)	75	61	81	72
Systemic Artery (SA)	84	92	81	84
Pressures, mm. Hg (mean)				
RA	15/9 (10)	11/4 (6)	10/2 (6)	9/5 (8)
RV	75/15 (32)	60/5 (22)	80–112/0–4 (36)	49–53/3–5 (20)
PA	75/40 (50)	—	80/32 (50)	39–42/28–34 (36)
Flows, L./min.				
Total pulmonary (TPBF)	6.1	3.5 (57)*	5.8	5.4 (93)*
Effective pulmonary	4.8	2.6 (54)*	4.5	2.9 (64)*
Systemic (SBF)	8.1	3.8 (47)*	6.5	4.9 (75)*
Left-to-right shunt	1.3	0.9 (69)*	1.3	2.5 (172)*
Right-to-left shunt	3.3	1.2 (36)*	2.0	2.0 (100)*
$\frac{\text{L to R}}{\text{TPBF}} \times 100$	21	26	22	46
$\frac{\text{R to L}}{\text{SBF}} \times 100$	41	32	31	41
Resistance dynes cm. sec.$^{-5}$				
Pulmonary	473	—	690	565
Systemic	1085	—	1115	1620
RV Pressure work, Kg./hr.	109	45	169	109
Stroke volume, ml.	82	37	71	69
Peripheral A-V O_2 difference, ml./L.	27	54	41	58

*Percent of preoperative value.

septum and right ventricular myocardium showed scars, and the endocardium was opaque. The auricular septum had a 5 x 5 cm. secundum type defect. Both atria contained friable clots. The lungs weighed 1,415 grams. The main pulmonary artery was dilated and larger than the aorta; the left pulmonary artery contained a large, organized, and partly calcified thrombus which extended into the smaller branches. Other old as well as recent thrombi were encountered in this distal pulmonary vasculature. Multiple small splenic and renal infarcts were present.

Microscopically, the myocardium showed old scar tissue and a partially organized old infract, as well as recent hemorrhage consistent with recent infarction. Right ventricular myocardial fibers were hypertrophied. The small arteries of the lungs disclosed old and recent thrombi, hypertrophy of smooth muscle, and intimal thickening.

Case 2, H. H. (SVAH 18853), was asymptomatic until the age of 22 years, when exertional dyspnea, orthopnea, and fatigue were noted following recovery from an attack of pneumonia. Atrial septal defect was demonstrated by cardiac catheterization at Walter Reed Hospital, on April 29, 1952; pulmonary artery pressure was reported to be 42/28 mm. Hg.

In March, 1955, electrocardiogram showed right heart strain. Chest film showed minimal right ventricular enlargement with prominent pulmonary artery. Angiocardiography demonstrated a dilated right heart and pulmonary artery. Pulmonary function was normal. Exercise tolerance was limited by dyspnea and fatigue; the physical fitness index was 2.6. Digitalis was prescribed without benefit. During cardiac catheterization, two anomalous pulmonary veins were found draining into the right atrium. Pulmonary hypertension of 80/30, mean 50 mm. Hg (Table I), and arterial O_2 saturation of 82 per cent were observed.

In an attempt to reduce right atrial pressure, and possible right-to-left shunting, ligation of the inferior vena cava below the renal veins performed on June 27, 1955, caused pain in the legs to become a major symptom, while respiratory complaints and venous pressure were essentially unaltered. On July 26, 1955, a Bailey-type atrioseptopexy was performed without clinical improvement.

Cardiac catheterization on Nov. 7, 1955, showed a significant increment in oxygen content of right atrial blood (Table I). Another operation on Jan. 18, 1956, showed that the inferior vena cava had been transposed inadvertently in the repair and was delivering blood through septal defect into the left atrium. The closure of septal defect had partially broken down, and the superior anomalous vein had not been transposed.

The superior pulmonary vein was then anastomosed to the inferior vein draining through the posterior chamber and septal defect into the left atrium, and the chest was closed. Pulmonary edema and hemorrhagic infarction of the right middle and right lower lobes ensued, and the patient died within a few hours.

At post-mortem examination the heart weighed 510 grams; there was marked right atrial and ventricular hypertrophy and dilatation. Two anomalous pulmonary veins from the right lung drained into the posterolateral aspect of the right atrium. A 2.5 x 2.5 cm. secundum type defect was present. The right ventricular wall was 5 to 8 mm. thick. The left atrium and ventricle were normal in size. Myocardial sectioning disclosed an apical scar extending into the anterior right ventricular wall. Total weight of the lungs was 2,075 grams.

Microscopically, there was patchy fibrosis of the myocardium of the left ventricle. Examination of the lungs showed moderate passive congestion in the right upper lobe, and hemorrhagic infarction of right, middle, and lower lobes. Vascular changes consisted of intimal thickening, hyperplastic mediosclerosis of medium size arteries, as well as old and recent thrombi.

RESULTS

1. *Clinical Status.*—Ligation of the inferior vena cava in E. I. resulted in a decrease in dyspnea. He became ambulatory, and despite considerable pain and edema in the legs, he was motivated to resume light part-time work. Less than 2 months later he again manifested progressive intractable heart failure, and died 6 months after operation. This course was compatible with the syndrome of chronic massive pulmonary artery thrombosis that was recently reviewed

by Ring and Bakke.[7] Autopsy showed fragmentation of fresh thrombi attached to an organized and calcified thrombotic lesion in the main branch of the left pulmonary artery.

The clinical effect of caval ligation in H.H. was development of pain and some edema of the legs, which further curtailed his ability for restricted ambulatory activities.

2. *Hemodynamic Changes.*—Right atrial and ventricular pressure declined in E. I., as did all calculated values for blood flow and stroke volume of the right ventricle (Table I). In H. H. right ventricular and pulmonary arterial pressures also diminished. The effective pulmonary blood flow and systemic blood flow decreased, but there was a negligible change in stroke volume. A-V oxygen difference increased in both patients. There was a slight increase in arterial oxygen saturation, a fall in hematocrit and pressure work of the right ventricle.

SUMMARY AND CONCLUSION

Ligation of the inferior vena cava below the renal veins in 2 patients with atrial septal defects and venoarterial shunting due to pulmonary hypertension resulted in slight and transient improvement in one patient with intractable heart failure, and reduced cardiac output, effective pulmonary blood flow and stroke work of the right ventricle in both patients. The clinical course was not substantially improved in either individual.

The authors gratefully acknowledge the considerable assistance of Doctors Edmund A. Kanar, David Dillard, and Prescott Jordon, Jr., who performed the surgery, and Doctors John R. Evans, David V. Brown, Wilbur Y. Hallet, Clyde R. Jensen, and Paul C. Griffith, who performed the meticulous autopsy examinations and studied the microscopic sections on these patients.

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FATAL MYOCARDITIS FOLLOWING SMALLPOX VACCINATION

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THE occurrence of encephalitis as a complication to smallpox vaccination is well known and has been discussed repeatedly elsewhere, but up to 1955, no case of acute myocarditis in association with smallpox vaccination had been published.

Dolgopol, Greenberg, and Aronoff,[1] in 1955, analyzed 49 alleged cases of encephalitis following smallpox vaccination of 5,000,000 persons in New York City in 1947. Forty-three cases with 2 deaths were accepted as postvaccination encephalitis. Another case was that of a man, aged 34 years, who 9 days after the vaccination suddenly developed severe headache followed by convulsions and death within an hour after admission to hospital. At necropsy the brain and all other organs showed marked congestion. Microscopic examination revealed a severe actue focal myocarditis with mononuclear inflammatory foci. The brain showed congestion and occasional small petechial hemorrhages. The diagnosis was acute focal myocarditis; congestive encephalopathy.

CASE REPORT

The following case was encountered during an investigation of the causes of death among Danish soldiers. It was reported on at the Ninth Scandinavian Congress of Military Medicine in Oslo, in November, 1954.[2]

A 22-year-old conscript, previously in perfect health, had undergone smallpox vaccination without complications as a child. He was revaccinated in the course of a routine mass vaccination. The response was strongly positive and was interpreted as a primary take. On the eighth day he was taken to the infirmary with a pronounced headache and a rectal temperature of 39.8° C. The pulse was raised "according to the temperature" but the actual pulse rate was not stated in the brief case report. Apart from paleness and a pronounced local reaction on the left shoulder with regional axillary lymphadenitis, nothing special was noted. No rash, angina faucium, or stiffness of the neck was present. Stethoscopic findings were negative. There were no psychic disturbances. Neither blood cell counts or electrocardiography was performed. The case was interpreted as a strong vaccination reaction, but was not considered dangerous. The following morning, however, the patient suddenly uttered a loud cry, was restless and unconscious, with a very rapid pulse. Death ensued within 5 minutes (10 days after the vaccination).

Autopsy.—Three crust-covered vaccination wounds, each 1 cm. in diameter, were noted on the left deltoid region but no old vaccination scars were found. The pericardial sack contained 40 ml. of serous exudate but was without fibrinous covering. The heart was of normal size, and nothing abnormal was noted in the endocardium, valves, or coronary arteries. The myocardium, however, especially in the left ventricle, was flabby and marbled, with pale and hyperemic areas interchanging. There was no myocardial fibrosis. All the organs, notably the lungs, were con-

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gested, but there were no signs of pneumonia. The spleen was about double the normal size. The dura was normal, whereas the leptomeninges were hyperemic, but without purulent exudate. The brain was not edematous and nothing abnormal was noted in it on examination.

Histologic examination of the myocardium revealed in several sections, notably from the left ventricle, numerous foci of acute degeneration with loss of transverse striation, granular necrosis of myofibrils, and pronounced infiltration with granulocytes and some lymphocytes. Between these areas normal myofibrils were found. In sections from the cerebral cortex and central ganglia no perivascular cellular infiltrations, indicative of encephalitis, were found. The meninges revealed no signs of inflammation.

The diagnosis at autopsy was acute myocarditis with slight hydropericardium and congestion of the organs, notably the meninges and the cerebral cortex.

COMMENT

A bacteriologic examination was not performed, but in the absence of any known infectious disease it seems most likely that the acute fatal myocarditis was a vaccination sequela. No other serious complications were reported in connection with the mass vaccination which was carried out with vaccine from the State Serum Institute, Copenhagen.

According to Danish legislation all children are vaccinated before school age. The patient had, furthermore, confirmed that he had been vaccinated against smallpox but did not know any details concerning this event. The response to the revaccination was not merely an accelerated reaction but was of the "primary take" type and no old scar was found. The fact that there was a history of vaccination in childhood does not rule out a primary reaction. Liao[3] found in a study of military recruits that 12.6 per cent of those with a history of vaccination more than 10 years previous were primary reactors at the revaccination. Usually, all severe reactions are associated with primary takes and are rare after accelerated responses.

The clinical course and autopsy findings in this case are quite analogous to the case of Dolgopol and associates[1] reported above. Death ensued on the ninth and tenth days, respectively. Swedish authors[4,5] have recently reported clinical and electrocardiographic evidence of 2 more, nonfatal cases of postvaccination myocarditis, and continued studies are in progress.[6]

The present case was of interest even from a forensic point of view. A compensation claim was raised, and as the deceased had been revaccinated during military service, the relatives were awarded compensation.

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Additions and Corrections

OBSERVATION ON THE DIRECT EFFECT OF DIGOXIN ON RENAL EXCRETION OF SODIUM AND WATER

(Am. Heart J. 52:592, 1956)

1. The weights of the dogs in this experiment are as follows:

Dog 1	8.3 Kg.	Dog 9	9.2 Kg.
Dog 2	10.2 Kg.	Dog 10	8.7 Kg.
Dog 3	9.7 Kg.	Dog 11	10.3 Kg.
Dog 4	7.4 Kg.	Dog 12	11.1 Kg.
Dog 5	8.7 Kg.	Dog 13	8.3 Kg.
Dog 6	9.1 Kg.	Dog 14	7.6 Kg.
Dog 7	8.3 Kg.	Dog 15	10.5 Kg.
Dog 8	8.4 Kg.	Dog 16	7.8 Kg.

Dog ascites—10.1 Kg. initially and with the development of the ascites it weighed 14.3 Kg.

2. The concentration of sodium should be meq./L. throughout.
3. The total sodium should be meq./10 min. interval.
4. The total creatinine should be in mg./10 min. intervals throughout.
5. Fig. 3,*F* as published was identical with Fig. 3,*C*. This was an error on our part and the correct Fig. 3,*F* is submitted herewith.

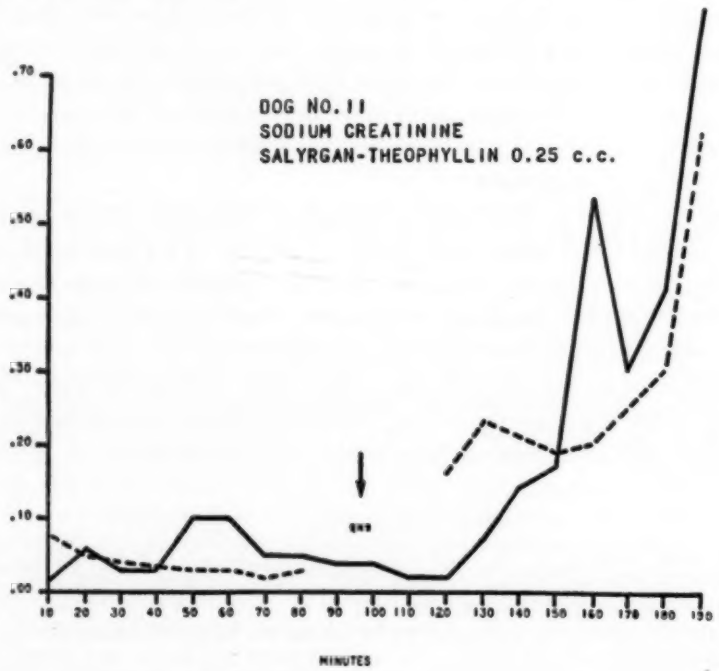

Fig. 3,F.

6. The broken and continuous lines have been reversed in Fig. 3,*A* through *F*.

William E. Jaques, M.D.
Albert S. Hyman, M.D.
Edward S. Hyman, M.D.

Book Reviews

REHABILITATION LITERATURE 1950-1955, A Bibliographic Review of the Medical Care, Education, Employment, Welfare, and Psychology of Handicapped Children and Adults. Compiled by Earl C. Graham and Marjorie M. Mullen, New York, 1956, Blakiston Company, 621 pages.

The appearance of a bibliography in book form is always a matter of rejoicing to those who need and use such keys to unlock the doors of information.

This bibliography comprises 5,214 references to books, articles in journals, journals, congresses, and pamphlets. Approximately one half of the references are identified with the medical and associated therapy fields. Of special interest to readers of the American Heart Journal are the 95 items relating to the heart.

The material, which is almost entirely in English, is arranged alphabetically by subject with an author index of 42 pages at the end. Five or six publications in English emanate from the Netherlands and Switzerland, but references to foreign language literature consist of only a few in French. Does this mean that much less is being published in other languages than in English on the subject of rehabilitation, or just that such material is beyond the scope of this bibliography?

Geographic breakdowns under each main heading show a few references under Canada, several under Europe and Asia, South Africa, Australia and New Zealand. Israel is included, as is Mexico, but not Russia. The majority of references are listed under the various states of the U.S.A.

It is to be hoped that this bibliography can be kept up to date and expanded. The preface states that it is supplemented by the monthly issues of *Rehabilitation Literature; Selected Abstracts of Current Publications of Interest to Workers with the Handicapped*, compiled by the library of the National Society for Crippled Children and Adults, Chicago.

M.G.H.

PERIPHERAL VASCULAR DISORDERS. Edited by Peter Martin, R. Beverley Lynn, J. Henry Dible, and Ian Aird, Edinburgh and London, 1956, E. & S. Livingstone, Ltd.; Baltimore, 1956, The Williams and Wilkins Company, 847 pages, 450 figures.

This book is comprehensive, profusely illustrated, extensively documented, and well indexed. The anatomy and physiology of the peripheral vessels as well as the clinical and laboratory techniques for studying the peripheral circulation are treated in unusual detail. Radiographic methods of diagnosis and surgical methods of treatment are stressed. The careful descriptions of the pathologic changes in specific diseases are outstanding.

The editors and the nine well-known authorities who contributed to this volume should be congratulated for having written an excellent reference book.

J. W. E.

ADRENAL FUNCTION IN INFANTS AND CHILDREN. A SYMPOSIUM. Edited by Lytt I. Gardner, New York, 1956, Grune & Stratton, Inc.

This interesting book contains the complete proceedings of a symposium held in 1954, in Syracuse, which brought together most of the prominent workers in the field of pediatric endocrinology. Its content, twenty-five articles on some of the most recent developments in the investigation of adrenocortical function in infancy and childhood, provides a broad view of physiologic as well as chemical and clinical problems related to this branch of medicine. The availability

of more precise biochemical methods opens up important aspects of human adrenal physiology. Such as heretofore complex clinical condition as the adrenogenital syndrome begins to be understood as a defect in the enzymatic systems which control the normal metabolism of corticosteroids. A particularly stimulating aspect of these reports deals with the attempt to study the adrenal function of premature and newborn infants.

The symposium will serve also as a valuable reference for those who need to evaluate the status of adrenal function in a wide variety of diseases, such as nephrosis and, possibly, rheumatic fever, where disturbances of pituitary adrenal relationships seem to play a significant, though ill-understood role.

C. G.

RADIOLOGY OF THE HEART AND GREAT VESSELS. By Robert N. Cooley, M.D., and Robert D. Sloan, M.D., Baltimore, 1956, The Williams & Wilkins Company, 309 pages, 195 illustrations.

This monograph is devoted to a description of the application of roentgenology to the study of the heart and great vessels, both in health and in disease. It was originally published as a chapter in a larger treatise on diagnostic roentgenology. The first portion is devoted to a description of technical procedures, including fluoroscopy, roentgenography, roentgenkymography, electrokymography, cardiac catheterization, angiocardiography, and aortography, as applied to these problems.

The middle section of the book is devoted to a description of the roentgen appearance of the normal heart and great vessels. The illustrations are clearly reproduced and well labeled. The provision of small diagrammatic drawings alongside each reproduction of a roentgenogram is helpful in the identification of the normal chambers and vessels of the heart. The latter portion of the book is devoted to a discussion of abnormalities of the circulatory system, including diseases of the pulmonary vascular system, rheumatic heart disease, congenital heart disease, and the degenerative types of heart disease. There are also brief sections on other types of acquired heart disease, such as those accompanying deficiency states, anemia, etc. For the most part, the reproductions of roentgenograms are of excellent character.

The section on congenital anomalies of the heart and great vessels is well written and illustrated and is fairly extensive. The section on angiography and aortography also is clearly illustrated and described. The portion dealing with electrokymography is very brief and serves only as an introduction to this subject. The authors state that this volume is primarily the product of their experiences in the daily practice of radiology in the diagnosis of cardiovascular abnormalities, and is not meant to be compendious. This volume will probably be of the greatest interest to roentgenologists, although internists, cardiologists, and cardiac surgeons will profit from a careful perusal of it.

H.E.H.

Announcement

A COURSE IN ELECTROCARDIOGRAPHIC INTERPRETATION FOR GRADUATE PHYSICIANS will be given at the Michael Reese Hospital, by Louis N. Katz, M.D. (Director of the Cardiovascular Department, Medical Research Institute) and associates. The class will meet daily from 9:00 A.M. to 5:00 P.M., August 19 through 31, 1957.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Margaret Stern, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.